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(54) Title: NEW DERIVATIVES OF OXAZOLIDINONES AS ANTIBACTERIAL AGENTS

(57) Abstract: This invention discloses new fluorquinolonic derivatives of oxazolidinones of general formula (I) and processes for obtaining them, the corresponding pharmaceutical compositions and use thereof for manufacturing a medicament for the treatment of microbial infections. These new compounds are useful as antibacterial agents. Formula (I). Furthermore phenalen-type compounds according to general formula (II) are disclosed. Formula (II).

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## NEW DERIVATIVES OF OXAZOLIDINONES AS ANTIBACTERIAL AGENTS

### Field of the invention

This invention relates to fluorquinolonic  
5 derivatives of oxazolidinones. The compounds are useful as  
antibacterial agents.

### Background of the invention

For some years now the pharmaceutical industry has  
10 not been pursuing the development of new antibacterial  
agents specifically directed at gram-positive bacteria  
such as *Staphylococci*, *Enterococci*, *Streptococci* and  
mycobacteria. The gram-positive bacteria have nevertheless  
taken on particular importance due to the fact that they  
15 have developed resistance at an alarming rate to the  
conventionally used antibiotics, thus becoming organisms  
difficult both to treat and to eradicate from hospital  
environments. Examples of such strains are the  
*Staphylococcus* resistant to *meticillin* (MRSA),  
20 *Enterococcus* resistant to *vancomycin* (VRE), *Staphylococcus*  
*epidermidis* resistant to *meticillin* (MRSE), *Staphylococcus*  
*pneumoniae* resistant to *penicillin* (PRSP), etc.

The oxazolidinonic antibacterial agents are the  
25 most recent class of synthetic drugs which show high  
activity against gram-positive organisms. Owing to their  
new action mechanism, these compounds are effective  
against both sensitive and resistant pathogens, including  
MRSA, MRSE and VRE.

30

Various antibacterial oxazolidinones have been  
described in the patent literature, for example, to cite  
some of them, in WO 9507271. WO 9323384, WO 9854161. WO  
9514684, WO 9721708, WO 9514684, WO 9730981. WO 9737980.

WO 9801447, WO 9912914, WO 9613502.

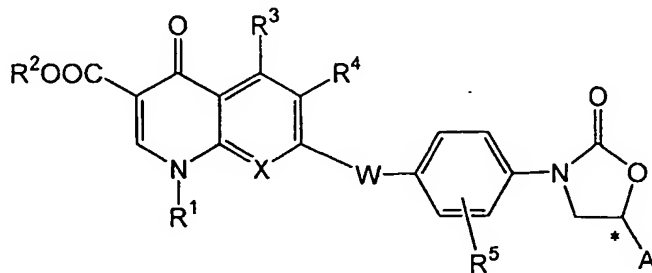
All these patents describe the oxazolidinones as compounds active against resistant gram-positive 5 organisms.

Owing to the constant appearance of new resistances, even to recently used antibiotics, it is desirable to develop powerful new antibiotics active 10 against the resistant strains, preferably with a broad antimicrobial spectrum.

This invention provides new derivatives of oxazolidinones, with a broad antimicrobial spectrum due to 15 their being active against gram-negative organisms while having improved activity against gram-positive organisms.

#### Description of the invention

20 The object of this invention are new fluorquinolonic derivatives of oxazolidinones of general formula (I):



25

(I)

in which:

X: CR<sup>6</sup> or N;

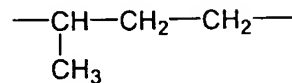
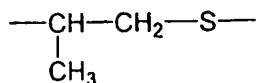
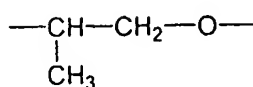
R<sup>1</sup>: alkyl C<sub>1</sub>-C<sub>4</sub>, cycloalkyl C<sub>3</sub>-C<sub>6</sub>, alkenyl C<sub>2</sub>-C<sub>4</sub>, 2-hydroxyethyl, 2-fluoroethyl, or phenyl optionally substituted by 1 or 2 atoms of fluorine;

R<sup>2</sup>: H, alkyl C<sub>1</sub>-C<sub>4</sub> or phenyl;

10 R<sup>3</sup>: H, halogen, alkyl C<sub>1</sub>-C<sub>4</sub>, or alkoxy C<sub>1</sub>-C<sub>4</sub>, amino;

R<sup>4</sup>: H or halogen;

15 R<sup>6</sup>: H, halogen, alkyl C<sub>1</sub>-C<sub>4</sub>, haloalkoxy C<sub>1</sub>-C<sub>4</sub>, or else R<sup>1</sup> and R<sup>6</sup> together form a bridge of structure



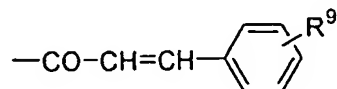
20 R<sup>5</sup>: H, halogen, OCH<sub>3</sub>, alkoxy C<sub>1</sub>-C<sub>4</sub>, alkyl C<sub>1</sub>-C<sub>4</sub>, or haloalkyl C<sub>1</sub>-C<sub>4</sub>;

A: -CH<sub>2</sub>-NH-R<sup>7</sup>, -CHOH-C≡CH;

25

in which

R<sup>7</sup>: isoxazol, -CO-R<sup>8</sup>, -CS-R<sup>8</sup>, -CS-OR<sup>8</sup>, -COOR<sup>8</sup>, -CONHR<sup>8</sup>, -CSNHR<sup>8</sup>, -SO<sub>2</sub>-R<sup>8</sup> or



30

in which

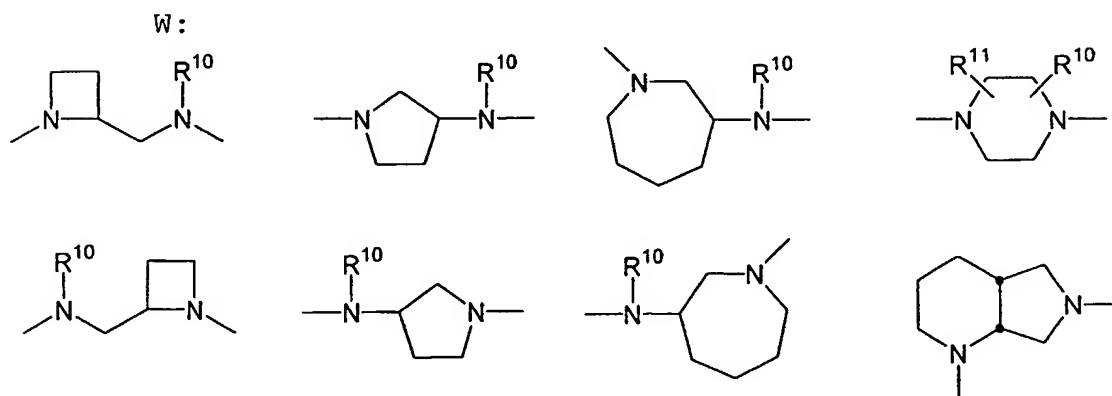
$R^8$ : alkyl  $C_1-C_4$ , haloalkyl  $C_1-C_4$ , alkenyl  $C_2-C_4$ , aryl, alkyl  $C_1-C_4$  substituted by an alkoxy group  $C_1-C_4$ , carboxyalkyl  $C_1-C_4$ , cyano, or amino, ...

5

$R^9$ : H, alkyl  $C_1-C_4$ , alkenyl  $C_2-C_4$ , OH, alkoxy  $C_1-C_4$ ,  $NR^{12}R^{13}$ ,  $NO_2$ , halogen, or  $CO-R^{12}$ ;

$R^{12}$  and  $R^{13}$ : independently, H or alkyl  $C_1-C_4$ ;

10



in which

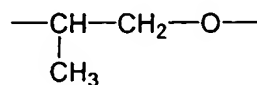
$R^{10}$  and  $R^{11}$  are independently H, or alkyl  $C_1-C_4$ ;

15

a pharmaceutically acceptable salt or solvate, or any geometric isomer, optical isomer or mixture of isomers thereof in any proportion or polymorph thereof.

20

Preferably,  $R^1$  is cyclopropyl, ethyl, 2-fluoroethyl, phenyl or difluorophenyl, or else  $R^1$  and  $R^6$  together form a bridge of structure:

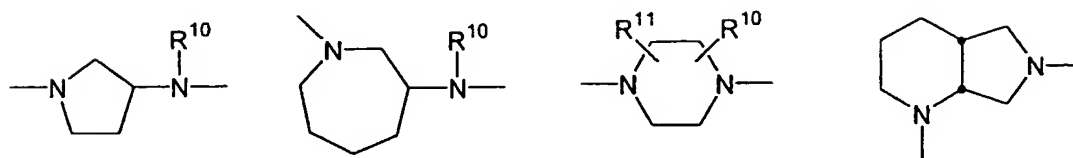


Preferably,  $R^6$  is H,  $CH_3$ ,  $OCH_3$ ,  $OCHF_2$ , F or Cl.  
More preferably,  $R^6$  is H or F.

Preferably,  $R^4$  is F or Cl and  $R^3$  is H.

5

Preferably, W is



in which  $R^{10}$  and  $R^{11}$  are as defined previously.

10

The compounds of the invention have a chiral centre in position C5 of the oxazolidinone ring. The preferred configuration of the C5 of the oxazolidinone ring is (S) for the compounds of formula (I) in which A = -  
15  $CH_2-NH-R^7$  and (R) for the compounds of formula (I) in which A = - $CHOH-C\equiv CH$ , in accordance with the Cahn-Ingold-Prelog nomenclature system.

Moreover, the compounds of formula (I) can contain  
20 other chiral centres. It is understood that the invention includes such optical isomers and diastereoisomers and mixtures thereof that possess antibacterial activity in any proportion.

25 The preferable compounds are selected from one of the following:

- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-  
30 fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

- 7-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-azepan-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 5 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 10 - 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid
- 9-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid
- 15 - 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid
- 20 - 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 25 - 1-cyclopropyl-7-[4-(4-{5-(S)-[(3-ethyl-ureido)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 1-cyclopropyl-7-(4-{4-[5-(S)-(ethoxycarbonylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 30 - 1-cyclopropyl-6-fluoro-7-{4-[2-fluoro-4-(5-(S)-{[3-(4-fluoro-phenyl)-acryloylamino]-methyl}-2-oxo-oxazolidin-

- 3-yl)-phenyl]-piperazin-1-yl}-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 1-cyclopropyl-7-[4-(4-{5-(S)-[(3-ethyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 5 - 1-(2,4-difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-5-[5-(R)-(1-(R,S)-hydroxy-prop-2-ynyl)-2-oxo-oxazolidin-3-yl]-phenyl}piperazin-1-yl)-4-oxo-1,4-dihydro-
- 10 [1,8]naphthyridine-3-carboxylic acid ethyl ester
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid ethyl ester
- 15 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid ethyl ester
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6,8-difluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 20 - 1-(2,4-Difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-(S)-(isoxazol-3-ylaminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-
- 25 [1,8]naphthyridine-3-carboxylic acid ethyl ester
- 1-(2,4-difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-(R)-(1-hydroxy-prop-2-ynyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]
- 30 naphthyridine-3-carboxylic acid
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid



- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid
- 5 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6,8-difluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 1-(2,4-Difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-
- 10 (S)-(isoxazol-3-ylaminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid
- 1-ethyl-6,8-difluoro-7-[4-(2-fluoro-4-{5-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-
- 15 carboxylic acid
- 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{2-oxo-5-(S)-[(3-propyl-thioureido)-methyl]-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-
- 20 carboxylic acid
- 1-cyclopropyl-6-fluoro-7-[4-{2-fluoro-4-[5-(S)-(methanesulfonylamino-methyl)-2-oxo oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 25 - 7-(4-{4-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-1-ethyl-6,8-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{2-oxo-5-(S)-[(2,2,2-trifluoro-acetylamino)-methyl]-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-
- 30 carboxylic acid
- 7-(4-{4-[5-(S)-(benzoylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro 4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.

- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
- 5 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3- carboxylic acid ethyl ester
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-  
10 difluoro-4-oxo-1,4-dihydro-quinoline-3- carboxylic acid methyl ester
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-  
15 difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3- carboxylic acid methyl  
20 ester
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-  
25 dihydro-6H-1-oxa-3a-aza-phenalen-5- carboxylic acid methyl ester
- 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-  
30 dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid ethyl ester
- 9-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-

- fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid methyl ester
- 9-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid ethyl ester
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  - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
  - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
  - 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
  - 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
  - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid methyl ester

- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6,8-difluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3- carboxylic acid methyl ester
- 5 - 1-Ethyl-6,8-difluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester

10           In this invention the term "a pharmaceutically acceptable solvate" is taken to mean a hydrate or solvate of an alcohol C<sub>1</sub>-C<sub>4</sub>.

          In this invention, the term "pharmacologically  
15 acceptable salts" includes salts of alkaline metals such as sodium or potassium and salts of alkaline earth metals such as calcium or magnesium, as well as acid-addition salts formed with inorganic and organic acids such as hydrochlorides, hydrobromides, sulphates, nitrates,  
20 phosphates, formiates, mesylates, citrates, benzoates, fumarates, maleates, lactates and succinates, among others.

          The pharmacologically acceptable salts are  
25 prepared by reaction of a compound of formula (I) with a suitable quantity of a base such as sodium, potassium, calcium or magnesium hydroxyde, or sodium methoxide, sodium hydride, potassium tert-butoxyde and the like in solvents such as ether, THF, methanol, ethanol, tert-  
30 butanol, isopropanol, dioxane, etc., or else in a mixture of solvents. The addition salts, where applicable, can be prepared by treatment with acids, such as hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, formic, methanesulphonic, citric, benzoic, fumaric, maleic, lactic

and succinic, in solvents such as ether, alcohols, acetone, THF, ethyl acetate, or mixtures of solvents.

The stereoisomers of this invention can be  
5 prepared by using reagents in a single enantiomeric form in processes where this is possible or by carrying out the reaction in the presence of reagents or catalysts in their single enantiomeric form or by resolution of mixtures of stereoisomers by conventional methods. Some of the  
10 preferred methods include resolution of diastereoisomeric salts formed with chiral acids such as mandelic, camphorsulphonic, tartaric acid and the like. Methods commonly used are included in Jaques et al. in "Enantiomers, Racemates and Resolution" (Wiley  
15 Interscience, 1981).

In the definitions of this invention, an alkyl group C<sub>1</sub>-C<sub>4</sub>, as a group or as part of a group, is taken to mean a lineal or branching alkyl group which contains up  
20 to 4 atoms of carbon. Thus it includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl.

Likewise, an alkoxy group C<sub>1</sub>-C<sub>4</sub> includes, for  
25 example, a methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy and tert-butoxy group.

An alkenyl group C<sub>2</sub>-C<sub>4</sub> includes, for example, a vinyl, allyl, propenyl and 1- butenyl, 2-butenyl and 3-  
30 butenyl group.

A haloalkyl group C<sub>1</sub>-C<sub>4</sub> means an alkyl group C<sub>1</sub>-C<sub>4</sub> substituted by one or more atoms of halogen, the same or different. It thus includes, for example, chloromethyl,

fluoromethyl, trifluoromethyl, chloroethyl, fluoroethyl, difluoroethyl, trifluoroethyl, fluoropropyl, chloropropyl, etc.

5           A haloalkoxy group C<sub>1</sub>-C<sub>4</sub> means an alkoxy group C<sub>1</sub>-C<sub>4</sub> substituted by one or more atoms of halogen, the same or different. Thus it includes, for example, chloromethoxy, fluoromethoxy, trifluoromethoxy, chloroethoxy, fluoroethoxy, difluoroethoxy, 10 trifluoroethoxy, fluoropropoxy, chloropropoxy, etc.

A cycloalkyl group C<sub>3</sub>-C<sub>6</sub> represents a cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl group.

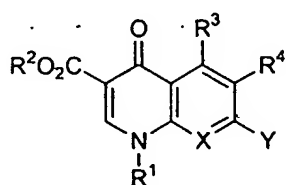
15           The term halogen, in this invention, refers to F, Cl, Br, I, preferably F and Cl.

The term aryl, in this invention, includes phenyl and naphthyl optionally substituted by up to five 20 substituents, the same or different, preferably up to two, in any position of the ring. Suitable substituents include halogen, amino, hydroxy, alkyl C<sub>1</sub>-C<sub>4</sub>, alkoxy C<sub>1</sub>-C<sub>4</sub>, phenyl.

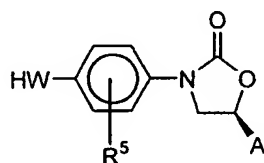
The compounds of this invention can be prepared in 25 various ways. They can be prepared by using the methods described below, together with methods known in the field of organic chemical synthesis, or by the variations that might be made thereto by an expert in the subject. Preferred methods include, but are not limited to, those 30 described below. The reactions are carried out in the solvents appropriate for the reagents and materials used and suited for the transformations carried out. An expert in organic synthesis will understand that the functional groups present in the molecule must be consistent with the

proposed transformations. This may in some cases require modifying the order of the synthesis steps or selecting one particular method rather than another, in order to obtain the desired compound of the invention. Moreover, in some of the procedures described below it may be desirable or necessary to protect the reagent functional groups present in the compounds or intermediates of this invention with conventional protecting groups. Various protecting groups and procedures for introducing them and removing them are described in Greene and Wuts (*Protective Groups in Organic Synthesis*, Wiley and Sons, 1999). All the references cited herein are incorporated integrally by reference.

The compounds of formula (I) can be obtained by reaction of a compound of formula (II), with a compound of formula (III):



(II)

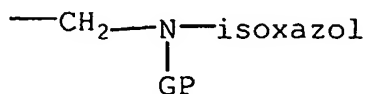


(III)

in which

A' is:

- a)  $-\text{CH}_2-\text{NH}-\text{R}^7$
- b)  $-\text{CHOH}-\text{C}\equiv\text{CH}$
- c)



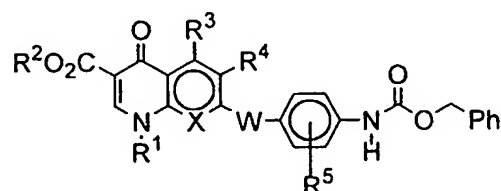
25

Y is an leaving group, such as an atom of halogen (F, Cl, Br, I), a tosylate or mesylate group and the like;  
 $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^5$ , X and W have the meaning defined

above;

GP is an amine protecting group.

Alternatively, the compounds of formula (I) in 5 which A= -CHOH-C≡CH can also be obtained by reaction of a compound of formula (IV) with 2,3-hydroxy-pent-4-ynyl p-toluenesulphonate:

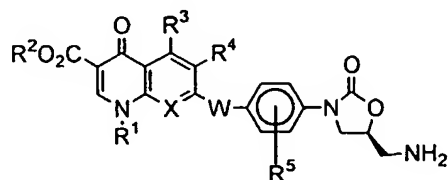


10

(IV)

in which R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, X and W have the meaning defined above.

The compounds of formula (I) in which A= -CH<sub>2</sub>-NH-R<sup>7</sup> 15 and R<sup>7</sup> is different from isoxazol, can also be obtained by reaction of a compound of formula (V):



(V)

20

in which R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, X and W have the meaning defined above, with a compound of formula (VI) or with a compound of formula (VII)

25

R<sup>7</sup>-L  
(VI)

R<sup>8</sup>-N=C=Z  
(VII)



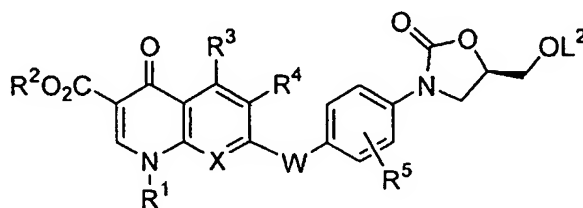
in which

L is a good leaving group, such as an atom of halogen (F, Cl, Br, I), a tosylate or mesylate group and the like;

Z is Oxygen or Sulphur, and

$R^7$  and  $R^8$  have the meaning defined above, with  $R^7$  being different from isoxazol.

10 The compounds of formula (I) in which  $A = -CH_2-NH-R^7$  and  $R^7$  is isoxazol can also be obtained by reaction of a compound of formula (VIII)



(VIII)

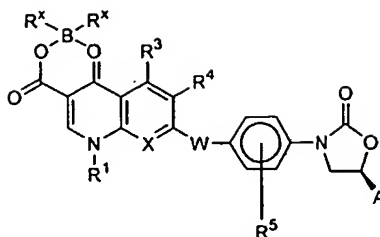
15 in which

-  $OL^2$  represents a good leaving group, such as a residue of aryl or methyl sulphonic acid, whether substituted or not substituted, preferably by a tosylate or mesylate group;

20 -  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ , X and W have the meaning defined above;

with isoxazolil-3-amine, with the amino group suitably protected with an amine protecting group, for example with Troc (2,2,2-trichloroethoxycarbonyl).

The compounds of formula (I), in which  $R^2 = H$  can also be obtained by hydrolysis of a boron chelate of formula (IX):



(IX)

in which

- 5         $R^x$  can be F or  $\text{CH}_3\text{COO}-$ ;  
       A,  $R^1$ ,  $R^3$ ,  $R^4$ ,  $R^5$ , X and W have the meaning defined  
 above.

And if required, after any of the methods  
 10 described herein, one or more of the following optional  
 steps can be carried out:

- Converting a compound of general formula (I)  
 into another compound of general formula (I);
- Eliminating any protecting group;
- 15        - Preparing a pharmacologically acceptable salt of  
 a compound of formula (I) and/or pharmacologically  
 acceptable solvate thereof.

The reaction of the compounds of formula (II) with  
 20 compounds of formula (III) is carried out in an organic  
 solvent in the presence of an organic base. Preferably the  
 reaction is carried out in solvents such as pyridine,  
 acetonitrile, dimethylformamide, N-methylpyrrolidone, etc.  
 in the presence of bases such as triethylamine, DBU,  
 25 diisopropylethylamine, etc.

The reaction of compounds of formula (IV) with  
 2,3-hydroxy-pent-4-ynyl p-toluenesulphonate is carried out  
 in an aprotic solvent such as N,N-dimethylformamide, THF,

preferably THF, at low temperature, preferably at  $-68^{\circ}\text{C}$ , and in the presence of a base such as n-butyllithium, lithium tert-butoxide, LDA, preferably in n-butyllithium.

5           The reaction of compounds of formula (V) with a compound of formula (VI) is carried out in an organic aprotic solvent such as acetonitrile, dichloromethane or pyridine or in a mixture of an organic solvent and water in the presence of a base. Preferably L is Cl, EtO, etc,  
10 so that  $\text{R}^7\text{-L}$  can be an acid, an acid chloride, an anhydride, an ester, a dithioester, an alkyl or aryl chloroformate, etc. The reaction of compounds of formula (V) with a compound of formula (VII) is preferably carried out in pyridine.

15

          The reaction of the compounds of formula (VIII) with isoxazolil-3-amine, with the amino group suitably protected, is carried out in an aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, preferably  
20 in N,N-dimethylformamide, at a temperature between 0 and  $70^{\circ}\text{C}$ , and in the presence of a strong base such as sodium hydride, lithium tert-butoxide, sodium tert-butoxide, potassium tert-butoxide or sodium amide, preferably sodium hydride.

25

          Hydrolysis of the compounds of formula (IX) can be carried out according to the methods previously described in the literature (Masuhiro Fujita Chem. Pharm. Bull. (1988), 46(5), 787-796, Joseph P. Sánchez J. Med.  
30 Chem. (1995), 38, 4478-4487)

          For  $\text{R}^x = \text{F}$ , the hydrolysis is carried out preferably in a mixture of alcohol-water in the presence of a base. As water-alcohol mixture it is preferable to

use ethanol-water or methanol-water and as base it is preferable to use an organic base such as triethylamine or another secondary or tertiary amine such as tributylamine, diisopropylethylamine, DBU, etc. The reaction is carried out at a temperature that can range between room temperature and the reflux temperature of the water-alcohol mixture. The reaction is carried out preferably at the reflux temperature of the water-alcohol mixture.

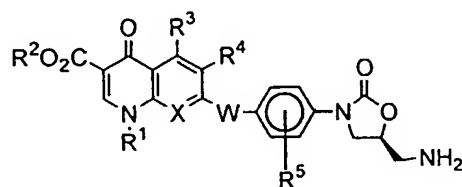
10           When  $R^* = \text{CH}_3\text{COO}$  the hydrolysis is carried out preferably in a mixture of an organic aprotic solvent and another protic solvent in the presence of a base. As aprotic solvent it is preferable to use acetonitrile and as protic solvent it is preferable to use water. As base  
15 it is preferable to use an inorganic base such as sodium, lithium or potassium hydroxide or sodium, lithium or potassium carbonate, etc.

A reaction of interconversion of a compound of  
20 formula (I) into another compound of formula (I) consists, for example, in hydrolysing a compound of formula (I) in which  $R^2$  is an alkyl  $\text{C}_1\text{-C}_4$  or phenyl radical to convert it into a compound of formula I in which  $R^2$  is hydrogen. The hydrolysis is carried out preferably in a water-alcohol  
25 medium preferably using as base an inorganic base. Still more preferably, the hydrolysis is carried out in ethanol-water or methanol-water, while sodium, lithium or potassium hydroxide is used as a base.

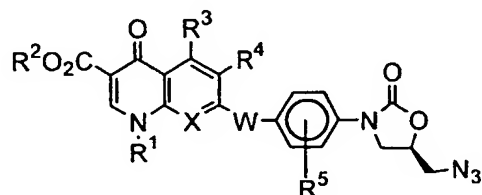
Another example of reaction of interconversion of  
30 a compound of formula (I) into another compound of formula (I) consists in the esterification of a compound of formula (I) in which  $R^2$  is hydrogen, to yield another compound of formula (I) in which  $R^2$  is an alkyl  $\text{C}_1\text{-C}_4$  or phenyl radical, by the conventional methods of

esterification described in the literature. For example, by reaction of a compound of formula  $R^2-OH$  with the compound of formula (I) in which  $R^2$  is hydrogen, having previously activated the carboxylic acid with carbonyl diimidazole, or else having previously converted the carboxylic acid into an acid chloride by reaction with thionyl chloride, or else having converted it into mixed anhydride by reaction with alkyl chloroformate.

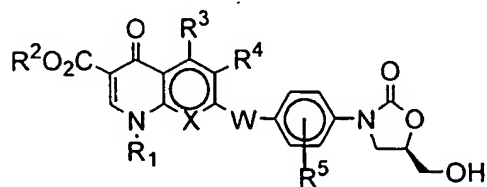
Also object of invention are the compounds of formula (V), (X) and (XI):



(V)



(X)



(XI)

in which  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $X$  and  $W$  have the meaning defined above. These compounds are useful as intermediates for making the compounds of formula (I) of

this invention.

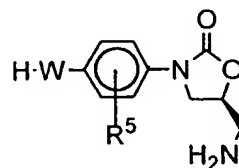
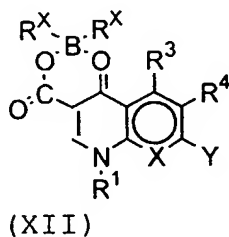
Described below are some of the procedures for making the intermediates used for preparing the compounds 5 of formula (I).

The compounds of formula (V), (X) and (XI) can be obtained in accordance with schemes 1A and 1B.

10 Thus, the compounds of formula (V) can be obtained:

a. by reaction of a compound of formula (II) or of formula (XII) with a compound of formula (XIII):

15



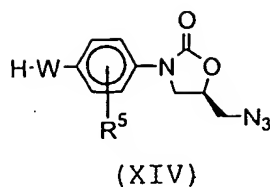
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The reaction can be carried out under the conditions described above for the reaction of a compound of formula (II) with a compound of formula (III);

b. by catalytic reduction of a product of formula 25 (X) or by reduction of the azide group chemically with triphenylphosphine, etc.

The compounds of formula (X) can in their turn be obtained:

30 a. by reaction of a compound of formula (XII) or of formula (II) with a compound of formula (XIV):

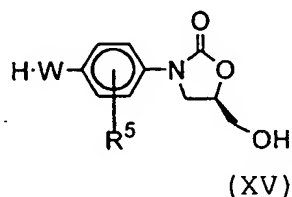


The reaction can be carried out under the conditions described above for the reaction of a compound of formula (II) with a compound of formula (III);

b. from a compound of formula (XI) by conversion of the hydroxyl group into a good leaving group, such as mesylate, tosylate or halogen and subsequent reaction with sodium azide.

The compounds of formula (XI) can in their turn be obtained:

a.- by reaction of a compound of formula (XII) or of formula (II) with a compound of formula (XV):



The reaction can be carried out under the conditions described above for the reaction of a compound of formula (II) with a compound of formula (III);

b.- by reaction of a compound of formula (IV) with (R)-glycidil butyrate. The reaction is carried out in an aprotic solvent such as N,N-dimethylformamide, THF, preferably THF, at low temperature, preferably at -68°C, and in the presence of a base such as n-butyllithium, lithium *tert*-butoxide, LDA, preferably in n-butyllithium.

Utilisation of the compounds of formula (XII) to obtain the three foregoing intermediates requires an additional step of hydrolysis of the boron chelate, as indicated in schemes 1A and 1B, which step is carried out under the conditions described above for hydrolysis of the compound of formula (IX).

The compounds of formula (VIII) can be obtained by reaction of a compound of formula (XI) with aryl or methyl sulphonyl chloride, substituted or not substituted, preferably with mesyl chloride or p-toluenesulphonyl chloride, in an aprotic solvent, such as methylene chloride, and in the presence of an organic base, such as triethylamine.

15

The compounds of formula (IX) can be obtained by reaction of a compound of formula (XII) with a compound of formula (III). The reaction can be carried out under the conditions described above for the reaction of a compound of formula (II) with a compound of formula (III).

The products of formula (II) and of formula (XII) are obtained according to the methods described in the literature. These products have been used as intermediates in the synthesis of quinolones and similar with antibacterial activity such as ciprofloxacin, ofloxacin, moxyfloxacin, norfloxacin, tosufloxacin, etc. (See patents WO 8807993, WO 8807998, WO 9006922, JP 59122470. JP 58029789, EP 0351889).

30

The compounds of formula (III), (XIII), (XIV) and (XV) can be obtained in accordance with scheme 2.

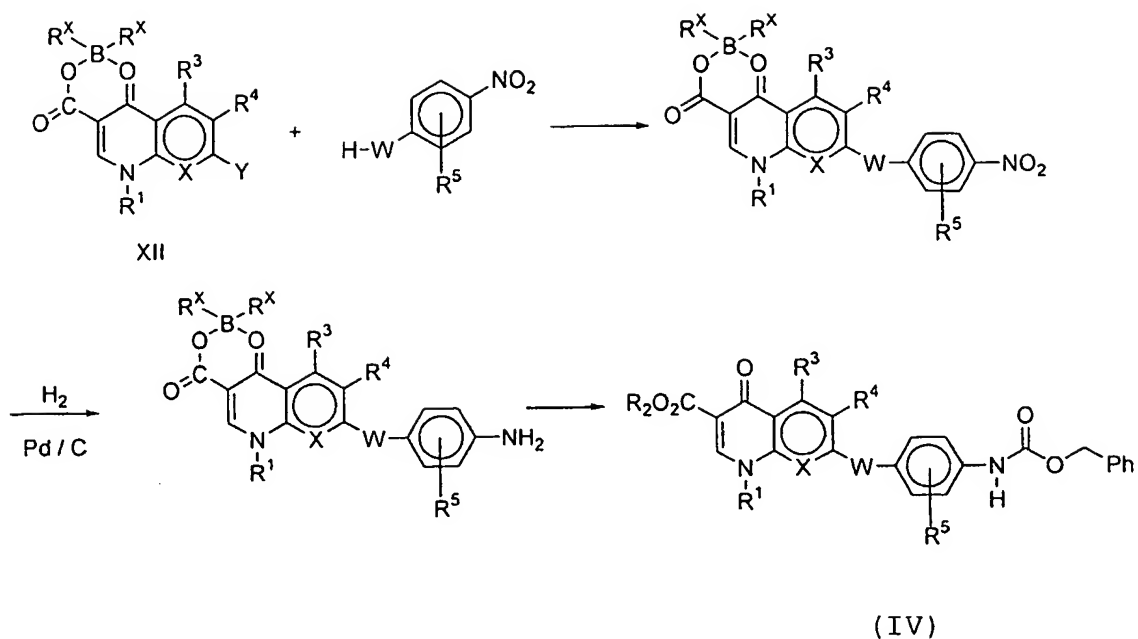


Thus, the compounds of formula (IIIa), (XIII) and (XIV) can be obtained from a compound of formula (XVI) by conversion of the hydroxyl group into an  $\text{NH}_2$ ,  $\text{N}_3$  or  $\text{NHR}^7$  group, in accordance with reactions well-known to an expert in organic chemistry.

The compounds of formula (IIIb) can be obtained by reaction of a compound of formula (XVII) with 2,3-hydroxy-pent-4-ynyl p-toluenesulphonate, under conditions analogous to those described for the reaction of a compound of formula (IV) with said reagent.

The compounds of formula (IIIc) can be obtained by reaction of a compound of formula (XVI) with isoxazolil-3-amine, with the amino group suitably protected, for example with Troc, and prior conversion of the hydroxyl group into a good leaving group, for example, mesylate, tosylate, halogen, etc.

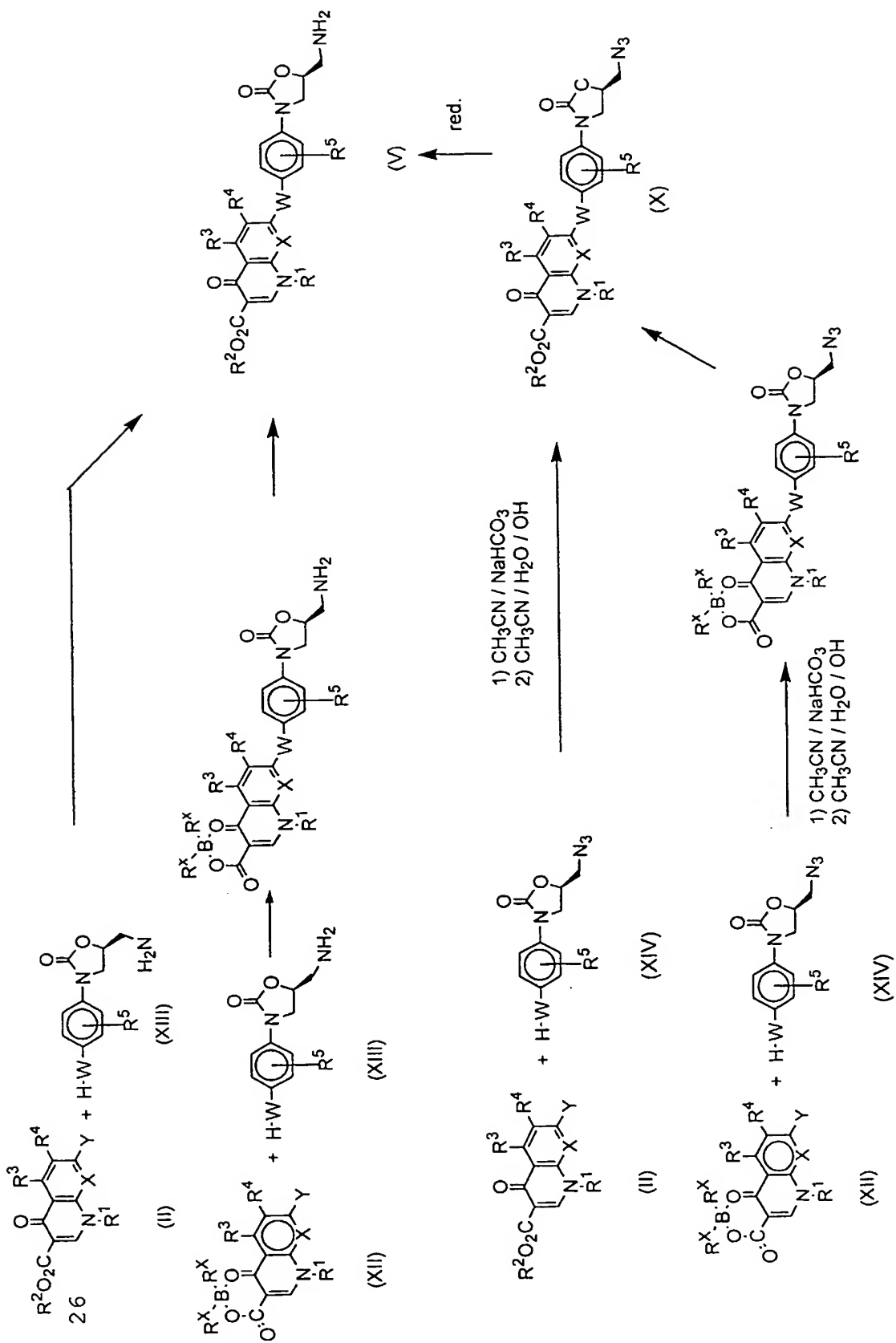
The compounds of formula (IV) can be obtained according to the following scheme:



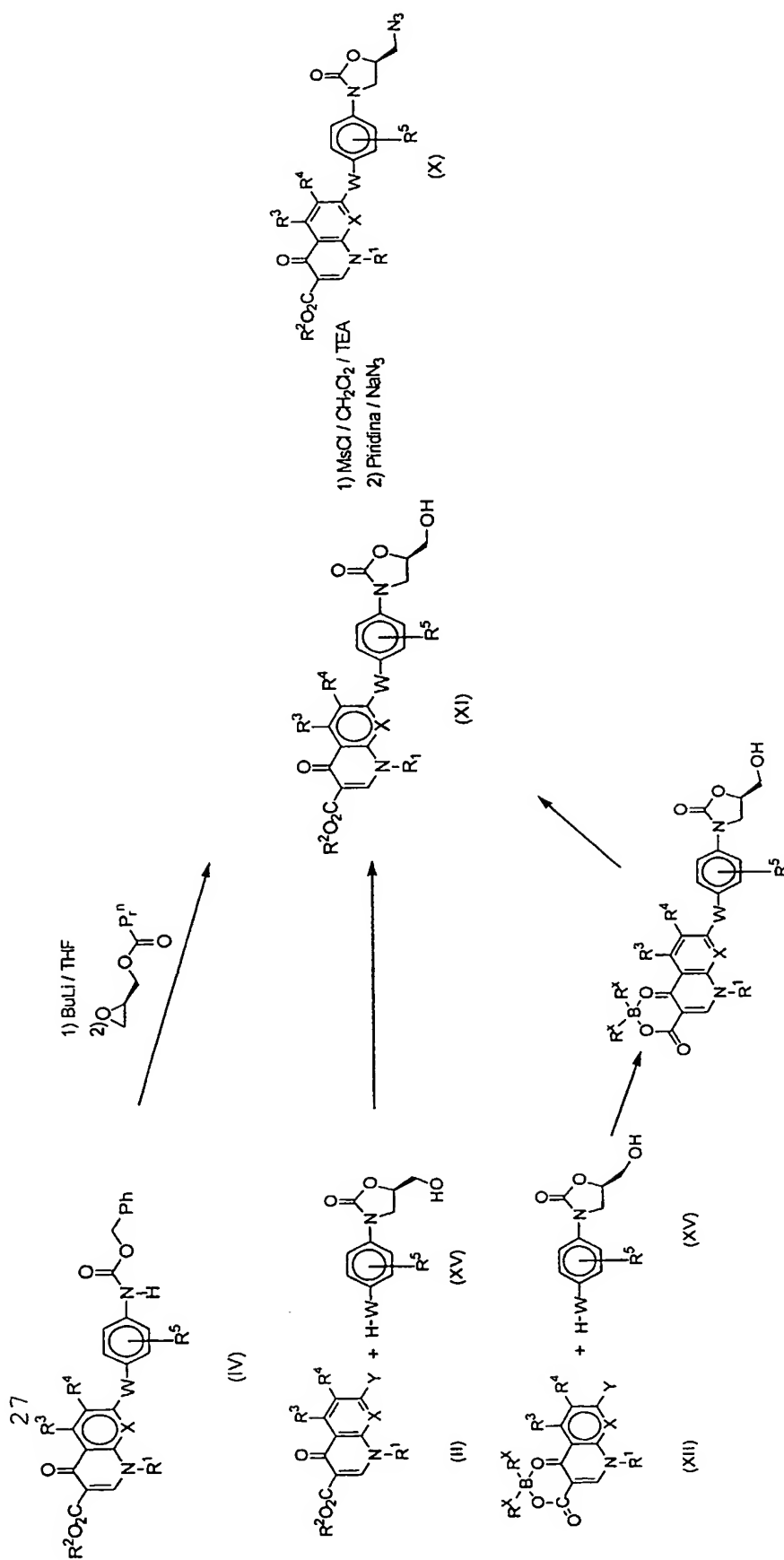
The reactions are carried out in suitable solvents, 5 and under conventional conditions. The schemes indicate the preferred reaction conditions.

The 2,3-hydroxy-pent-4-ynyl p-toluenesulphonate is obtained according to the procedure described in EP 10 1029854A1.

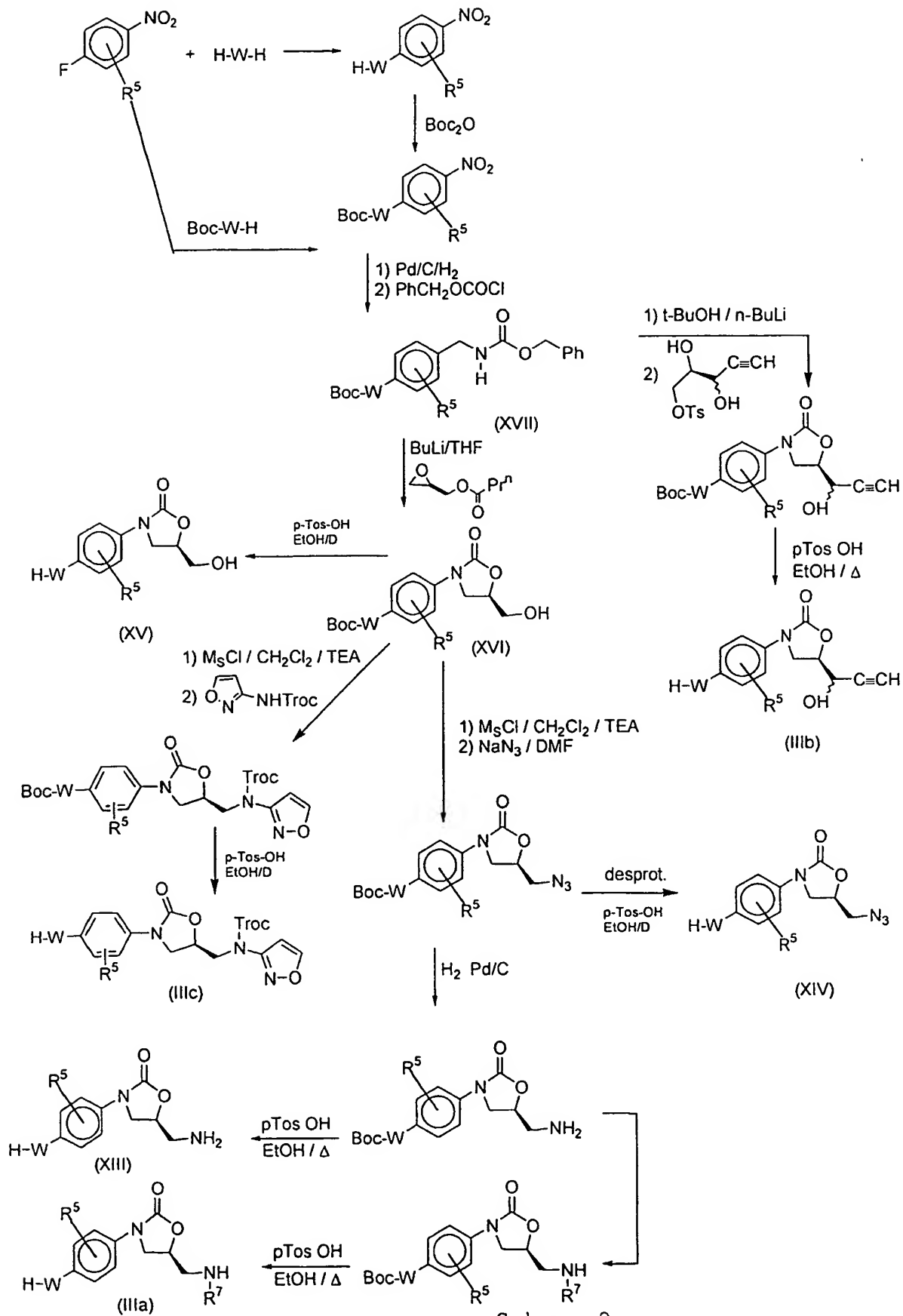
The compounds of formula (VI) and of formula (VII) are commercial, are extensively described in the literature or can be prepared by methods analogous to 15 those known in the state of the art from products commercially available.



Scheme 1A



Scheme 1B



Also object of this invention are compositions which include a compound of general formula (I), a pharmaceutically acceptable salt or solvate, or any geometric isomer, optical isomer or mixture of isomers  
5 thereof in any proportion or polymorph thereof, in a therapeutically active quantity and a suitable quantity of at least one pharmacologically acceptable excipient.

The compositions of the invention can be  
10 formulated in solid or liquid form following the conventional pharmaceutical techniques. The solid formulations include tablets, capsules, sachets, powders, suppositories, etc. The excipients can include diluents, disintegrators, wetting agents, lubricants, colourants,  
15 flavourings or other conventional adjuvants. The typical solid excipients include, for example, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium stearate or sodium lauryl sulphate. The liquid compositions include solutions, suspensions or emulsions.  
20 They can consist in solutions in water or in water-propyleneglycol or water-polyethylenglycol systems, also optionally containing flavourings, colourants, stabilisers and thickeners.

25 The compositions can be administered orally, parenterally or topically.

The compounds of formula (I) show activity as antibacterial agents. Advantageously they possess a broad  
30 spectrum of activity against gram-positive bacteria such as *Staphylococcus*, *Streptococcus*, *Enterococcus* and the like, as well as against gram-negative bacteria such as *E. Coli*, *H. Influenzae*, *M. catarrhalis*, etc., and even against strains resistant to known antibiotics such as

meticillin, vancomicine, penicillin, etc. They are also active against anaerobic microorganisms such as *Bacteroides fragilis*. Also object of this invention, therefore, is the use of a compound of formula (I) for making a pharmaceutical composition for the treatment of microbial infections, in humans or warm-blooded animals.

Below, and by way of non-restrictive explanation of the invention, the following examples are set out.

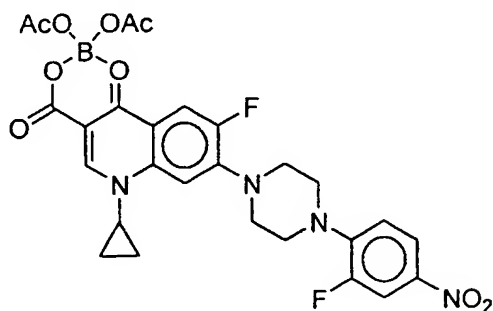
## 10 EXAMPLES OF SYNTHESIS

### PREPARATION OF INTERMEDIATES

#### Reference Example No.1:

1-Cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-nitro-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid diacethoxyboron chelate

20



To 10 g (0.024 mol) of 1-cyclopropyl-7-chloro-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid diacethoxyboron chelate (obtained according to WO 8807998) in 150 ml of acetonitrile are added 5.4 g (0.024 mol) of 1-(2-fluoro-4-nitro-phenyl)piperazine (obtained according to the method described by S.J. Brickner and col. J. Med. Chem. 1996, 39, 673-679) and 2 g (0.024 moles) of sodium bicarbonate.

The reaction is heated to reflux for 48 h. It is concentrated to dryness and the residue is treated with 100 ml of water and extracted with 3 x 100 ml of

dichloromethane. The organic phase is dried and concentrated and the residue is chromatographed on silica gel.

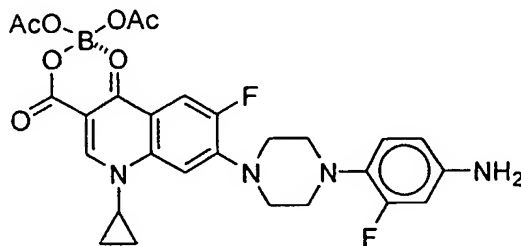
Elution with dichloromethane/ethanol 98/2 yields 6.7 g of the product of the title.

$^1\text{H}$ -RMN: ( $\text{CDCl}_3$ , 200 MHz,  $\delta$ ppm): 9,08 (s, 1H); 8,14 (d, 1H); 8,10-7,94 (s.c., 2H); 7,56 (d, 1H); 7,01 (t, 1H); 3,82-3,75 (m, 1H); 3,75-3,50 (s.c., 8H); 2,04 (s, 6H); 1,64-1,30 (s.c., 4H).

Reference Example No.2:

7-[4-(4-amino-2-fluoro-phenyl)piperazin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid diacethoxyboron chelate.

20



To 6.7 g (0.011 mol) of the product obtained in the previous example, in 50 ml of dimethylformamide, are added 0.7 g of 10% Pd/C paste and it is placed under hydrogen atmosphere at 40°C and atmospheric pressure. When the reaction has finished it is filtered over decalite and the decalite washed with 20 ml of DMF.

30

The filtrate liquids are poured onto 700 ml of water and extracted with 3 x 200 ml of dichloromethane. The organic phase is concentrated to dryness and the residues chromatographed on silica gel.

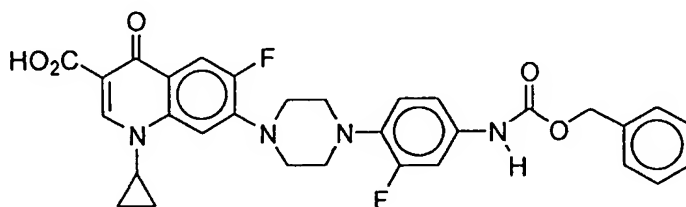


Elution with dichloromethane-ethanol 95/5 yields 2.6 g of the product of the title as yellow solid.

<sup>1</sup>H-RMN (CDCl<sub>3</sub>, 200 MHz, δ(ppm)): 9,04 (s, 1H); 8,10 (d, 1H); 7,45 (d, 1H); 6,84 (dd, 1H); 6,44-6,36 (s.c., 2H); 3,79-3,64 (m, 1H); 3,62-3,56 (s.c., 4H); 3,24-3,16 (s.c., 4H); 2,05 (s, 6H); 1,80-1,20 (s.a., 2H, NH<sub>2</sub>); 1,58-1,24 (s.c., 4H).

**Reference Example No.3:**

7-[4-(4-benzyloxycarbonylamino-2-fluoro-phenyl)-piperazin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.



To 2.62 g (4.58 mmol) of the product obtained in the previous reference example in 30 ml of THF and 10 ml of water is added 0.4 g (5 mmol) of sodium bicarbonate.

Onto the previous solution is added dropwise 0.8 g (5 mmol) of benzyl chloroformate and is maintained with stirring for 48 h. It is concentrated to dryness, 50 ml of water are added and it is extracted with 3 x 75 ml of dichloromethane.

The organic phase is dried and concentrated. The residue is stirred with 10 ml of dichloromethane for 10 minutes and the precipitate obtained is filtered.

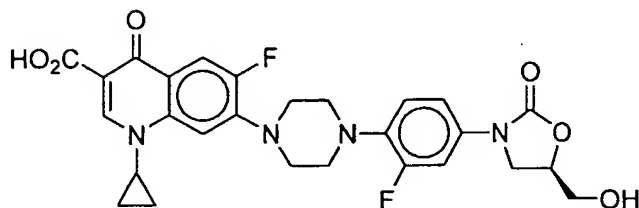
2 g of the product of the title are obtained thereby.

$^1\text{H}$ -RMN (DMSO, 200 MHz,  $\delta$  (ppm)): 9,84 (s.a., 1H); 8,64 (s, 1H); 7,92 (d, 1H); 7,61 (d, 1H); 7,50-7,30 (s.c., 6H); 7,22-7,01 (s.c., 2H); 5,18 (s, 2H); 3,92-3,78 (s.a., 5 1H); 3,70-3,10 (s.c., 8H); 1.42-1.10 (s.c., 4H).

**Reference Example No.4:**

1-cyclopropyl-6-fluoro-7-{4-[2-fluoro-4-5-(R)-hydroxymethyl-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-  
10 yl}-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.

15



20 To 2.2 g (3.7 mmol) of the product obtained in the previous preparation in 60 ml of THF cooled to  $-78^\circ\text{C}$  is added dropwise 3 ml (7.14 mmol) of n-butyllithium 2.5 M in hexane.

25 The reaction is maintained at  $-78^\circ\text{C}$  for 1 h and then 0.51 g (3.57 mmol) of (R)-glycidil butirate dissolved in 10 ml of THF are added.

It is allowed to reach room temperature and stirred thus  
30 for 16 h.

20 ml of saturated solution of ammonium chloride is added and it is concentrated until the THF is removed. 50 ml of

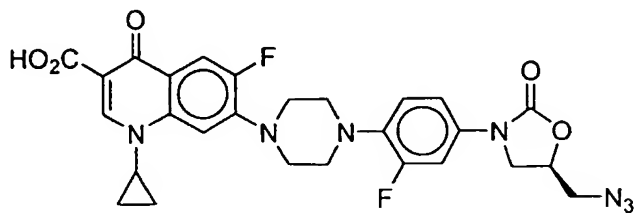
water are added and this is extracted with 3 x 100 ml of dichloromethane-ethanol (90/10).

The organic phase is dried and concentrated. The residue is chromatographed on silica gel. Elution with dichloromethane-ethanol (90/10) yields 0.5 g of the product of the title.

$^1\text{H}$ -RMN (DMSO- $d_6$ , 200 MHz,  $\delta$  (ppm)): 8,70 (s, 1H); 7,96 (d, 1H); 7,70-7,36 (s.c., 3H); 7,30-7,10 (s.c., 2H); 5,20-5,10 (s.a., 1H); 4,8-4,64 (m, 1H); 4,20-4,04 (m, 1H); 3,92-3,14 (s.c., 11H); 1,43-1,16 (s.c., 4H).

Reference Example No.5:

15 7-{4-[4-(5-(R)-azidomethyl-2-oxo-oxazolidin-3-yl)-2-fluoro-phenyl]-piperazin-1-yl}-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



20

Method 1:

To 0.5 g (0.92 mmol) of the product obtained in the previous preparation in 10 ml of dry dichloromethane is added 2.6 ml of triethylamine and it is then cooled to 0°C. 1.4 ml of methanesulphonyl chloride is added and this is then stirred at 0°C for 1 h.

It is poured onto water-ice(30 ml/20 g) saturated with sodium bicarbonate and the organic phase is decanted. It is dried on sodium sulphate, filtered and concentrated.

5 To the residue is added 10 ml of dimethylformamide and 1.17 g of sodium azide. This is heated to 75°C and stirred at this temperature for 16 h.

It is poured onto 100 ml of water and extracted with 3 x 10 100 ml of ethyl acetate. The organic phase is dried and concentrated and the residue is chromatographed on silica gel. Elution with dichloromethane-ethanol (90/10) yields 40 mg of the product of the title.

#### 15 Method 2:

To 1.5 g (4.7 mmol) of 5-(R)-azidomethyl-3-(3-fluoro-4-piperazin-1-yl-phenyl)-oxazolidin-2-one (Reference Example No.19) and 1.9 g (4.7 mmol) of acid 1-cyclopropyl-7-20 chloro-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid diacethoxyboron chelate (obtained according to WO 8807998) in 60 ml of acetonitrile is added 0.4 g (4.7 mmol) of sodium bicarbonate and this is heated to reflux for 48 h.

25

It is concentrated to dryness and the residue is treated with 100 ml of water and extracted with 3 x 100 ml of CH<sub>2</sub>Cl<sub>2</sub>. The organic phase is dried and concentrated and the residue is chromatographed on silica gel.

30

Elution with CH<sub>2</sub>Cl<sub>2</sub>/EtOH 95/5 yields 1.1 g of the product of the title as diacetoxiboron chelate.

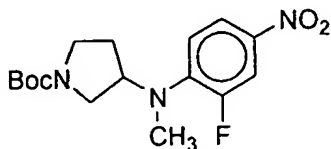
The 1.1 g thus obtained is dissolved in a mixture of 28 ml of water, 28 ml of acetonitrile and 8 ml of sodium hydroxide 1N. This is stirred at room temperature for 3 h, the acetonitrile is concentrated and 8 ml of hydrochloric acid 1N is added.

The precipitated solid is filtered, yielding 0.6 g of product identical to that obtained by method 1.

$^1\text{H}$ -RMN ( $\text{CDCl}_3$ , 200 MHz,  $\delta$  (ppm)): 8,79 (s, 1H); 8,01 (d, 1H); 7,54-7,24 (s.c., 2H); 7,16-6,90 (s.c., 2H); 4,83-4,70 (m, 1H); 4,42-4,34 (m, 1H); 4,10-3,20 (s.c., 12H); 1.44-1.12 (s.c., 4H)

**Reference Example No.6:**

15 3(R,S) - [(2-fluoro-4-nitro-phenyl) -methylamino] -  
pyrrolidine-1-carboxylic acid tert-butyl ester



To 7 g (0.0375 mol) of 3(R,S)-methylamino-pyrrolidine-1-carboxylic acid tert-butyl ester and 4.11 ml (0.0375 mol) of 3,4-difluoronitrobenzene in 80 ml of DMF is added 3.15 g of sodium bicarbonate and this is heated at 45°C for 16  
25 h.

It is poured onto 800 ml of water and extracted with 3 x 300 ml of AcOEt. The organic phase is dried and concentrated and the residue is chromatographed on silica  
30 gel.

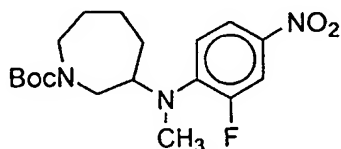
Elution with dichloromethane-ethanol 95/5 yields 7.9 g of the product of the title.

$^1\text{H}$ -RMN ( $\text{CDCl}_3$ , 200 MHz,  $\delta$  (ppm)): 8,00-7,88 (s.c, 2H); 6,88 (dd, 1H); 4,45-4,30 (m, 1H); 3,75-3,50 (s.a., 4H); 3,45-3,25 (s.c, 4H); 2,95 (s, 3H); 2,18-2,07 (m, 5 2H); 1.49 (s, 9H).

Reference Example No.7:

3( R, S)-[(2-fluoro-4-nitro-phenyl)-methyl-aminol]-azepan-1- carboxylic acid tert-butyl ester.

10



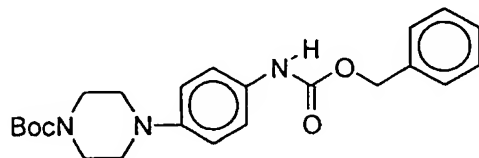
Following the previous procedure and using 3(R,S)-  
15 methylamino-azepan-1-carboxylic acid tert-butyl ester, the product of the title is obtained.

$^1\text{H}$ -RMN ( $\text{CDCl}_3$ , 200 MHz,  $\delta$  (ppm)): 8,10-7,80 (m, 2H); 6,90 (dt, 1H); 4,05-3,10 (m, 5H); 2,94 (m, 3H); 1.50  
20 and 1.41 (s, 9H); 1.20-2,10 (m, 6H).

Reference Example No.8:

4-(4-Benzyloxycarbonylamino-phenyl)-piperazin-1- carboxylic acid tert-butyl ester.

25



30

To 72.7 g (0.236 mol) of 4-(4-nitro-phenyl)-piperazin-1- carboxylic acid tert-butyl ester (WO 9725323), in 600 ml of THF and 125 ml of water is added 7.27 g of 10% Pd/C

paste and it is placed under atmosphere of hydrogen at atmospheric pressure and room temperature.

When reduction of the nitro group has been completed (thin-layer chromatography eluted with heptane/AcOEt 1/1),  
5 21 g (0.25 mol) of sodium bicarbonate and 40.2 g (0.236 mol) of benzyl chloroformate are added at 0°C.

It is shaken for 30 min at 0°C and filtered over decalite. The decalite is washed with 300 ml of THF and the filtrate  
10 liquids are concentrated until the THF has been removed.

200 ml of water is added and 3 x 200 ml of dichloromethane is extracted. The organic phase is dried and concentrated and the residue is chromatographed on silica gel.

15

Elution with heptane/AcOEt yields 69.8 g (72%) of the product of the title.

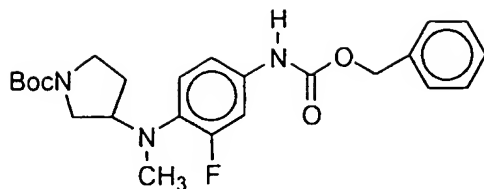
20

<sup>1</sup>H-RMN (CDCl<sub>3</sub>, 200 MHz, δ (ppm)): 7,42-7,24 (s.c., 7H); 6,86 (d.2H); 6,64 (s.a., 1H); 5,18 (s, 2H); 4,60-4,50 (s.c., 4H); 3,10-3,00 (s.c., 4H); 1.46 (s, 9H).

Using the procedure described above the following products  
25 are obtained:

**Reference Example No.9:**

3(R, S) - [(4-benzyloxycarbonylamino-2-fluoro-phenyl) - methyl-amino] - pyrrolidine-1- carboxylic acid tert-butyl  
30 ester.



5

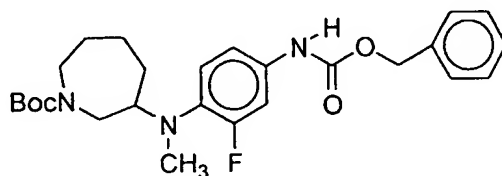
$^1\text{H}$ -RMN ( $\text{CDCl}_3$ , 200 MHz,  $\delta$  (ppm)): 7,42-7,26 (s.c. 6H); 7,01-6,92 (s.c., 3H, 2H aromatic + NH); 5,19 (s, 2H); 3,86-3,65 (m, 1H); 3,60-3,36 (s.c., 3H); 3,36-3,12 (s.c., 2H); 2,71 (s, 3H); 2,10-1,75 (s.c., 2H); 1,42 (s, 9H).

10

**Reference Example No.10:**

3(R, S) - [(4-benzylloxycarbonylamino-2-fluoro-phenyl) - methyl-amino] - azepan-1-carboxylic acid tert-butyl ester.

15



20

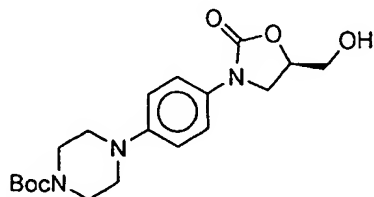
$^1\text{H}$ -RMN ( $\text{CDCl}_3$ , 200 MHz,  $\delta$  (ppm)): 7,60-7,20 (m, 5H); 7,20-6,80 (m, 3H); 3,95-2,90 (m, 5H); 2,71 (s, 3H); 1,45 and 1,37 (s, 9H); 1,05-2,00 (m, 6H).

25

**Reference Example No.11:**

4 - [4 - (5 - (R) - hydroxymethyl-2-oxo-oxazolidin-3-yl)phenyl] - piperazin-1-carboxylic acid tert-butyl ester.

30





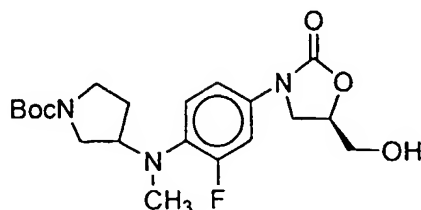
Following a procedure analogous to that of Reference Example No.4 and using 69.2 g (0.169 mol) of the product obtained in Reference Example No.8, 44.4 g (70%) of the product of the title is obtained.

<sup>1</sup>H-RMN (CDCl<sub>3</sub>, 200 MHz, δ (ppm)): 7,42 (d, 2H); 6,92 (d, 2H); 4,80-4,64 (s.c., 1H); 4,02-3,90 (s.c., 3H); 3,80-3,64 (m, 1H); 3,62-3,72 (s.c., 4H); 3,14-3,04 (s.c., 4H); 2,77 (t, 1H, OH); 1.45 (s, 9H).

As in the previous preparation, and following the procedure described in Reference Example No.4, the following products are obtained:

**Reference Example No.12:**

3-(R, S)-{[2-fluoro-4-(5-(R)-hydroxymethyl-2-oxo-oxazolidin-3-yl)-phenyl]-methyl-amino}-pyrrolidine-1-carboxylic acid tert-butyl ester.

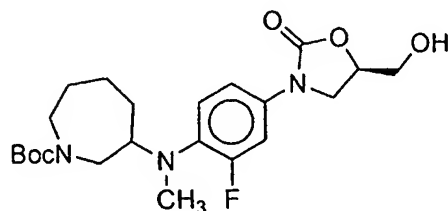


25

<sup>1</sup>H-RMN (CDCl<sub>3</sub>, 200 MHz, δ (ppm)): 7,41 (dd, 1H); 7,14-7,00 (s.c., 2H); 4,80-4,64 (m, 1H); 4,02-3,64 (s.c., 5H); 3,62-3,40 (s.c., 2H); 3,38-3,18 (s.c., 2H); 2,78 (s.a., 1H, OH); 2,70 (s, 3H); 2,06-1.80 (s.c., 2H); 1.42 (s, 9H).

## Reference Example No.13:

3 - (R, S) - { [2-fluoro-4 - (5 - (R) -hydroxymethyl-2-oxo-oxazolidin-3-yl) -phenyl] -methyl-amino} -azepan-1-carboxylic acid tert-butyl ester.

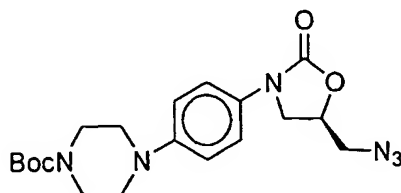


$^1\text{H}$ -RMN ( $\text{CDCl}_3$ , 200 MHz,  $\delta$  (ppm)): 7,95 (m, 1H); 7,40 (dd, 1H); 7,10 (m, 1H); 4,75 (m, 1H); 4,10-3,00 (m, 9H); 2,73 and 2,76 (s, 3H); 1.39 and 1.46 (s, 9H); 1.20-2,00 (m, 6H).

Following the procedure described in method 1 of Reference Example No.5 and using respectively the products obtained in reference examples 11 to 13, the following products are obtained:

## Reference Example No.14:

4 - [4 - (5 - (R) -azidomethyl-2-oxo-oxazolidin-3-yl) -phenyl] -piperazin-1-carboxylic acid tert-butyl ester.



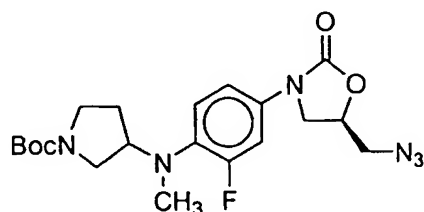
$^1\text{H}$ -RMN ( $\text{DMSO}-d_6$ , 200 MHz,  $\delta$  (ppm)): 7,44 (d, 2H); 7.02 (d, 2H); 4,96-4,84 (m, 1H); 4,17 (t, 1H); 3,84-3,62 (s.c., 2H); 3,56-3,30 (s.c., 5H); 3,17-3,04 (s.c., 4H); 1.42 (s, 9H).

## Reference Example No.15:

3-(R, S)-{[4-(5-(R)-azidomethyl-2-oxo-oxazolidin-3-yl)-2-fluoro-phenyl]-methyl-amino}-pyrrolidine-1-carboxylic acid tert-butyl ester.

5

10

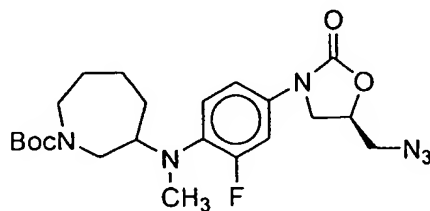


$^1\text{H}$ -RMN ( $\text{CDCl}_3$ , 200 MHz,  $\delta$  (ppm)): 7,41 (dd, 1H); 7,16-7,01 (s.c., 2H); 4,86-4,72 (m, 1H); 4,06 (t, 1H); 3,95-3,40 (s.c., 6H); 3,38-3,17 (s.c., 2H); 2,73 (s, 3H); 2,10-1.73 (s.c., 2H); 1.45 (s, 9H).

## Reference Example No.16:

3-(R, S)-{[4-(5(R)-azidomethyl-2-oxo-oxazolidin-3-yl)-2-fluoro-phenyl]-methyl-amino}-azepan-1-carboxylic acid tert-butyl ester.

25



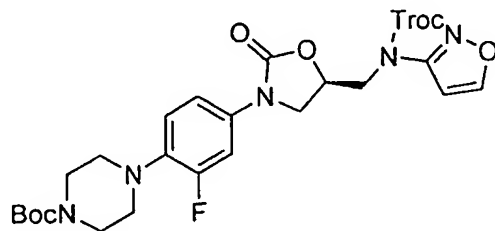
$^1\text{H}$ -RMN ( $\text{CDCl}_3$ , 200 MHz,  $\delta$  (ppm)): 7,35 (m, 1H); 7,20-6,80 (m, 2H); 4,75 (m, 1H); 4,05 (t, 1H); 3,95-3,00 (m, 8H); 2,74 (m, 3H); 2,00-1.00 (m, 6H); 1.46 and 1.39 (s, 9H).

## Reference Example No.17:

4-[2-Fluoro-4-(5-(R)-{[isoxazol-3-yl-(2,2,2-trichloroethoxycarbonyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-phenyl]-piperazin-1-carboxylic acid tert-butyl ester.

5

10



3.4 g (13 mmol) of 3-(2,2,2-trichloroethoxycarbonylamino)-isoxazol (prepared according to WO 0021960) is dissolved in 100 ml of DMF, and 536 mg (14.3 mmol) of sodium hydride (60% paste) is added in portions and stirred for 30 minutes. 6 g (12.7 mmol) of 4-{2-Fluoro-4-[2-oxo-5-(R)-(toluene-4-sulphonyloxymethyl)-oxazolidin-3-yl]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester (obtained according to US 5547950) is then added dissolved in 30 ml of DMF.

The reaction is heated to 90°C for 20 h. It is allowed to cool and is poured onto 500 ml of water. It is extracted with 3x250 ml of a 4/1 mixture of toluene/ethyl acetate. The organic phase is dried and concentrated and the residue is chromatographed on silica gel.

Elution with Heptane/Ethyl acetate 7/3 yields 2.5 g of the product of the title.

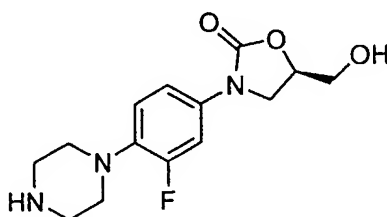
$^1\text{H}$ -RMN ( $\text{CDCl}_3$ , 200 MHz,  $\delta$  (ppm)): 8,34 (d, 1H); 7,45 (dd, 1H); 7,12 (m, 1H); 6,95 (m, 2H); 5,15 (m, 1H);

4,90 (m, 2H); 4,50 (dd, 1H); 4,25 (dd, 1H); 4,13 (t, 1H);  
3,85 (dd, 1H); 3,60 (m, 4H); 3,00 (m, 4H); 1.49 (s, 9H).

Reference Example No.18:

5        3-(3-Fluoro-4-piperazin-1-yl-phenyl)-5-(R)-  
         hydroxymethyl-oxazolidin-2-one

10



To 5 g (0.0126 mol) of 4-[2-fluoro-4-(5-(R)-  
15 hydroxymethyl-2-oxo-oxazolidin-3-yl)-phenyl]-piperazin-1-  
carboxylic acid tert-butyl ester (obtained according to US  
5547950) in 100 ml of ethanol is added 2.6 g (0.0139 mol)  
of para-toluenesulphonic acid and this is heated to reflux  
for 16 h. It is concentrated to dryness and the residue is  
20 chromatographed on silica gel (80 g) to the upper part of  
which alumina (20 g) is added.

Elution with dichloromethane/ethanol/ammonium  
hydroxide (90/10/1%) yields 1.6 g of the product of the  
25 title.

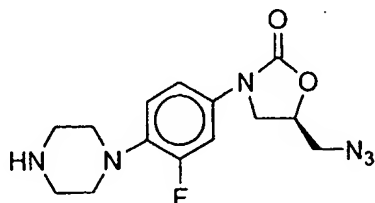
$^1\text{H}$ -RMN ( $\text{CDCl}_3$ , 200 MHz,  $\delta$  (ppm)): 7,50 (d.d., 1H);  
7,24-7,00 (s.c, 2H); 4,70 (m, 1H); 4,04 (t, 1H); 3,82-3,42  
(s.c, 3H); 2,86 (s.a, 8H).

30

## Reference Example No.19:

5-(R)-azidomethyl-3-(3-fluoro-4-piperazin-1-yl-phenyl)-oxazolidin-2-one.

5



10

To 5 g (0.011 mol) of 4-[4-(5-(R)-azidomethyl-2-oxo-oxazolidin-3-yl)-phenyl]-piperazin-1-carboxylic acid tert-butyl ester (obtained according to US 5547950) in 100 ml of ethanol is added 2.4 g (0.013 mol) of p-toluenesulphonic acid.

It is heated to reflux for 16 h. Once the reaction has ended it is concentrated to dryness and the residues pass through a column of silica gel (100 g) containing 25 g of alumina in the upper part.

Elution with dichloromethane/ethanol/ammonium hydroxide (80/20/1%) yields 3.5 g of the product of the title.

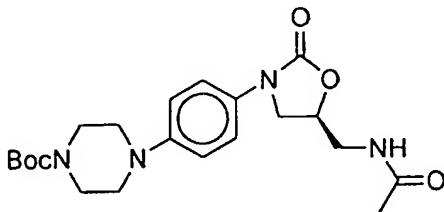
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$^1\text{H}$ -RMN ( $\text{CDCl}_3$ , 200 MHz,  $\delta$  (ppm)): 7,42 (dd, 1H); 7,10 (dd, 1H); 6,94 (t, 1H); 4,84-4,76 (m, 1H); 4,05 (t, 1H); 3,83-3,50 (s.c, 3H); 3,03 (s, 3H).

## Reference Example No.20:

4-{4-5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl}-phenyl}-piperazin-1-carboxylic acid tert-butyl ester.

5



10

To 40 g (0.0668 mol) of the product of Reference Example No.14 in 1,000 ml of ethyl acetate is added 4 g of 10% Pd/C paste and it is placed under atmosphere of hydrogen at atmospheric pressure and room temperature. When reduction of the azide group has finished (thin-layer chromatography), it is cooled to 0°C and 8.4 ml (0.103 mol) of pyridine and 13.4 ml (0.103 mol) of acetic anhydride are added.

20

It is stirred at 0°C for 30 min and then for 16 h at room temperature. It is filtered over decalite and the filtration liquids are concentrated to dryness.

25 The residue is chromatographed on silica gel. Elution with dichloromethane/ethanol 95/5 yields 27 g (97%) of the product of the title.

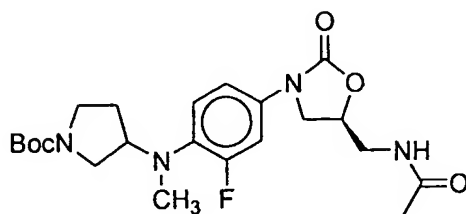
$^1\text{H}$ -RMN (DMSO, 200 MHz,  $\delta$  (ppm)): 8,30 (t, 1H, NH); 7,41 (d, 2H); 7,00 (d, 2H); 4,80-4,60 (m, 1H); 4,10 (t, 1H); 3,72 (t, 1H); 3,55-3,38 (s.c., 6H); 3,15-3,03 (s.c., 4H); 1.83 (s, 3H); 1.42 (s, 9H).

Following the procedure described above and using the products of reference examples No. 15 and No. 16, the following products are obtained:

5           **Reference Example No.21.**

3-(R, S)-({4-5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-methyl-amino)-pyrrolidine-1-carboxylic acid tert-butyl ester.

10



15

$^1\text{H}$ -RMN ( $\text{CDCl}_3$ , 200 MHz,  $\delta$  (ppm)): 7,41 (dd, 1H); 7,10-7,00 (s.c., 2H); 6,61 (t, 1H, NH); 4,82-4,70 (m, 1H); 4,02 (t, 1H); 3,97-3,40 (s.c., 6H); 3,40-3,18 (s.c., 2H); 2,75 (s, 3H); 2,10-1,80 (s.c., 2H); 1.42 (s, 9H).

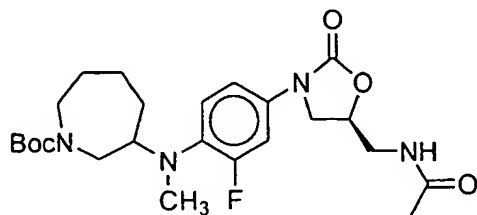
20

**Reference Example No.22.**

3-(R, S)-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-azepan-1-carboxylic acid tert-butyl ester.

25

30



$^1\text{H}$ -RMN ( $\text{CDCl}_3$ , 200 MHz,  $\delta$  (ppm)): 7,35 (dd, 1H); 7,15-6,85 (m, 2H); 6,45 (m, 1H); 4,75 (m, 1H); 4,01 (t,

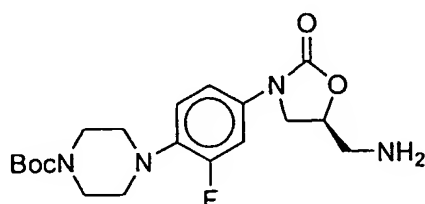


1H); 3,90-3,00 (m, 8H); 2,76 and 2,23 (s, 3H); 2,03 (s, 3H); 1,46 and 1,39 (s, 9H); 2,00-1,10 (m, 6H).

Reference Example No.23.

5 4-[4-(5-(S)-aminomethyl-2-oxo-oxazolidin-3-yl)-2-fluoro-phenyl]-piperazin-1-carboxylic tert-butyl ester.

10



To 30 g (0.071 mol) of 4-[4-(5-(R)-azidomethyl-2-oxo-oxazolidin-3-yl)-phenyl]-piperazin-1-carboxylic acid tert-butyl ester (obtained according to US 5547950) in 300 ml of ethanol is added 3 g of 10% Pd/C paste and it is placed under atmosphere of hydrogen at atmospheric pressure and room temperature. When the reaction has finished (thin-layer chromatography eluted with dichloromethane-ethanol 95/5) it is filtered over decalite and the decalite washed with 50 ml of ethanol.

The filtering liquids are concentrated to dryness and the residue is chromatographed on silica gel.

Elution with dichloromethane/ethanol/ammonium hydroxide 90/10/1% yields 14 g (50%) of the product of the title.

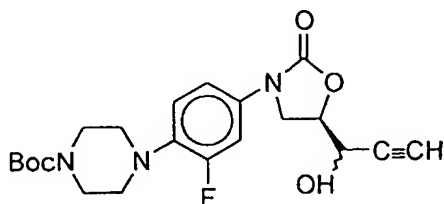
30

$^1\text{H}$ -RMN ( $\text{CDCl}_3$ , 200 MHz,  $\delta$  (ppm)): 7,47 (dd, 1H); 7,13 (dd, 1H); 6,94 (t, 1H); 4,75-4,60 (m, 1H); 4,01 (t, 1H); 3,82 (dd, 1H); 3,62-3,51 (s.c., 4H); 3,20-2,90 (s.c., 6H); 1.50 (s, 9H); 1.40 (s.a., 2H,  $\text{NH}_2$ ).

## Reference Example No.24.

4-{2-fluoro-4-[5-(R)-(1-(R,S)-hydroxy-prop-2-ynyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-carboxylic acid tert-butyl ester.

5



10

To 2.4 g (32.2 mmol) of tert-butanol in 30 ml of dry tetrahydrofuran, cooled to  $-10^{\circ}\text{C}$ , is added 9.2 ml (23 mmol) of n-Buli (2.5 M in hexane).

15 It is stirred for 30 min and allowed to reach a temperature of  $0^{\circ}\text{C}$ . 4.49 g (10 mmol) of 4-(4-benzyloxycarbonylamino-2-fluoro-phenyl)-piperazin-1-carboxylic acid tert-butyl ester (obtained according to US 5547950) is then added, dissolved in 10 ml of dry  
20 dimethylformamide.

After stirring for 10 min at  $0^{\circ}\text{C}$ , 3.4 g (12.5 mmol) of 2,3-hydroxy-pent-4-ynyl p-toluenesulphonate (obtained according to EP 1029854 A1) dissolved in 5 ml of DMF is  
25 then added dropwise.

It is allowed to reach room temperature and stirred for 16 h. It is poured onto 200 ml of saturated solution of sodium bicarbonate and extracted with 3 x 150 ml of ethyl  
30 acetate. The organic extracts are washed with 150 ml of water. The organic phase is dried and concentrated and the residue is chromatographed on silica gel.

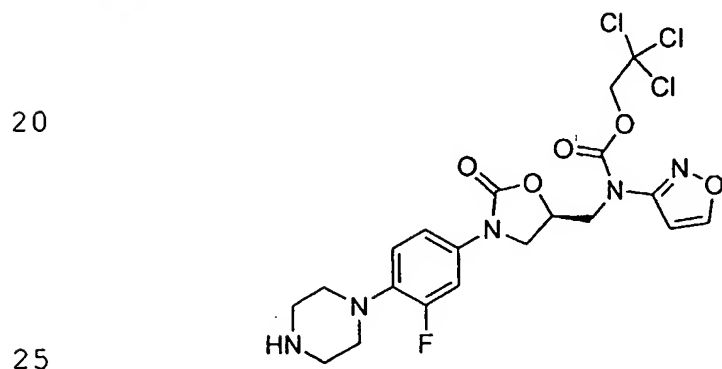
Elution with ethyl acetate/heptane 1/1 yields 2.6 g (62%) of the product of the title.

$^1\text{H}$ -RMN ( $\text{CDCl}_3$ , 200 MHz,  $\delta$  (ppm)): 7,45 (dd, 1H); 5 7,15 (m, 1H); 6,95 (t, 1H); 4,75 (m, 2H); 4,30-2,90 (m, 3H); 3,60 (m, 4H); 3,00 (m, 4H); 2,53 (d, 1H); 1.48 (s, 9H).

Following the procedure described in reference 10 examples 18 and 19 and using respectively the compounds obtained in reference examples 17 and 20 to 24 the following products are obtained:

**Reference Example No.25.**

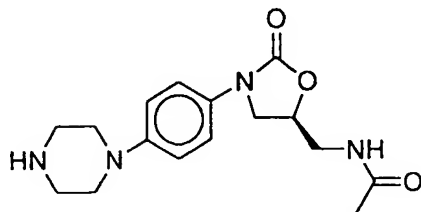
15 [3-(3-Fluoro-4-piperazin-1-yl-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-isoxazol-3-yl-carbamate of 2,2,2-trichloro-ethyl



$^1\text{H}$ -RMN ( $\text{CDCl}_3$ , 200 MHz,  $\delta$  (ppm)): 8,34 (d, 1H); 7,42 (dd, 1H); 7,10 (dd, 1H); 6,95 (m, 2H); 5,15 (m, 1H); 4,95 (m, 2H); 4,52 (dd, 1H); 4,25 (dd, 1H); 4,12 (t, 1H); 30 3,80 (dd, 1H); 3,12 (m, 8H).

## Reference Example No.26.

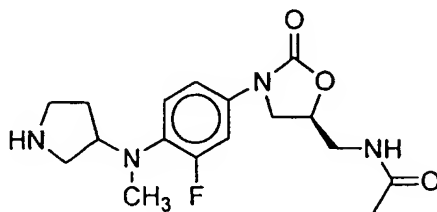
N-[2-oxo-3-(4-piperazin-1-yl-phenyl)-oxazolidin-5-(S)-ylmethyl]acetamide.



$^1\text{H}$ -RMN (DMSO- $d_6$ , 200 MHz,  $\delta$  (ppm)): 8,30 (t, 1H, NH); 7,41 (dd, 2H); 7,00 (dd, 2H); 4,80-4,60 (m, 1H); 4,06 (t, 1H); 3,71 (dd, 1H); 3,42 (t, 2H); 3,30-3,10 (s.c., 8H); 1.82 (s, 3H).

## Reference Example No.27.

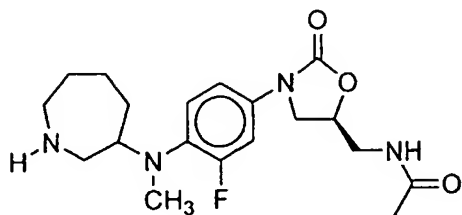
N-{3(R,S)-[3-fluoro-4-(methyl-pyrrolidine-3-yl-amino)-phenyl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide.



$^1\text{H}$ -RMN ( $\text{CDCl}_3$ , 200 MHz,  $\delta$  (ppm)): 7,39 (dd, 1H); 7,10-6,97 (s.c., 2H); 6,49 (t, 1H, NH); 4,83-4,70 (m, 1H); 4,02 (t, 1H); 3,90-3,60 (s.c., 4H); 3,13-2,80 (s.c., 4H); 2,72 (s, 3H); 2,02 (s, 3H); 2,00-1.65 (s.c., 2H).

## Reference Example No.28.

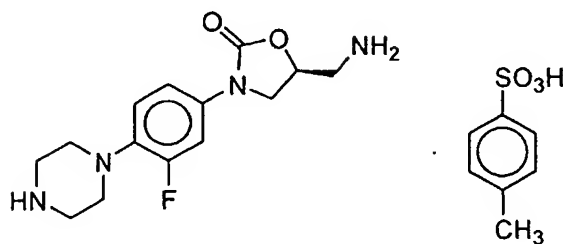
N-{3(R,S)-[4-(azepan-3-yl-methyl-amino)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide.



<sup>1</sup>H-RMN (CDCl<sub>3</sub>, 200 MHz, δ (ppm)): 7,35 (dd, 1H); 7,05 (m, 1H); 6,90 (t, 1H); 6,75 (t, 1H, NH); 4,75 (m, 1H); 4,00 (t, 1H); 3,90-3,30 (m, 4H); 3,20-2,60 (m, 4H); 2,72 (s, 3H); 2,30 (s.a., 1H); 2,02 (s, 3H); 1.90-1.00 (m, 6H).

## Reference Example No.29.

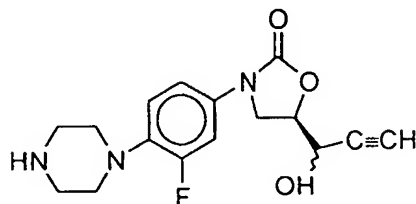
p-toluenesulphate of 5-(S)-aminomethyl-3-(3-fluoro-4-piperazin-1-yl-phenyl)-oxazolidin-2-one.



<sup>1</sup>H-RMN (DMSO-d<sub>6</sub>, 200 MHz, δ (ppm)): 7,56 (dd, 1H); 7,50 (d, 2H); 7,22-7,06 (s.c., 4H); 4,90-4,74 (m, 1H); 4,14 (t, 1H); 3,84-3,76 (m, 1H); 3,25-3,05 (s.c., 10H); 2,26 (s, 3H).

## Reference Example No.30.

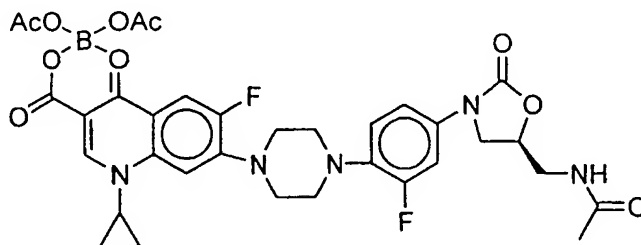
3-(3-fluoro-4-piperazin-1-yl-phenyl)-5-(R)-(1-(R,S)-hydroxy-prop-2-ynyl)-oxazolidin-2-one.



$^1\text{H}$ -RMN (DMSO- $d_6$ , 200 MHz,  $\delta$  (ppm)): 7,50 (m, 1H); 7,20 (m, 1H); 7,03 (m, 1H); 6,15 (s.a., 1H); 4,70 (m, 1H); 4,52 (m, 1H); 4,10 (t, 1H); 3,85 (m, 1H); 3,25 (m, 1H); 3,23 (s.a., 1H).

## Reference Example No.31:

7-(4-{-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid diacethoxyboron chelate.



To 1 g (3 mmol) of N-[3-(3-Fluoro-4-piperazin-1-yl-phenyl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide (obtained according to US 5547950) in 30 ml of acetonitrile are added 1.22 g of 7-chloro-1-cyclopropyl-6-

fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid diacethoxyboron chelate (obtained according to WO 8807998) and 0.43 ml (3 mmol) of triethylamine.

5 The reaction is heated to reflux for 16 h. It is concentrated to dryness and the residue is chromatographed on silica gel.

Elution with dichloromethane/ethanol 90/10 yields 0.8 g of 10 the product of the title.

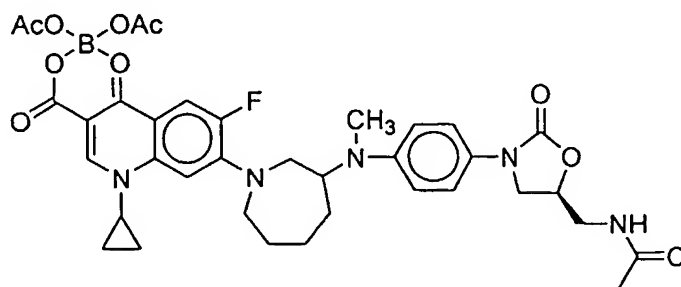
$^1\text{H}$ -RMN ( $\text{CDCl}_3$ , 200 MHz,  $\delta$  (ppm)): 9,04 (s, 1H); 8,10 (d, 1H); 7,56-7,44 (s.c., 2H); 7,08 (dd, 1H); 6,97 (t, 1H); 6,38 (t, 1H, NH); 4,82-4,68 (m, 1H); 4,01 (t, 15 1H); 3,90-3,56 (s.c., 8H); 3,30-3,20 (s.a., 4H); 2,04 (s, 6H); 2,02 (s, 3H); 1.90-1.20 (s.c., 2H).

#### Reference Example No.32.

7- [3- (R,S) - ({4- [5- (S) - (acetylamino-methyl) -2-oxo-  
20 oxazolidin-3-yl] -2-fluoro-phenyl} -methylamino) -azepan-1-yl] -1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid diacethoxyboron chelate.

25

30



Following the procedure of the previous example and using the product obtained in Reference Example No. 28, the product of the title is obtained.

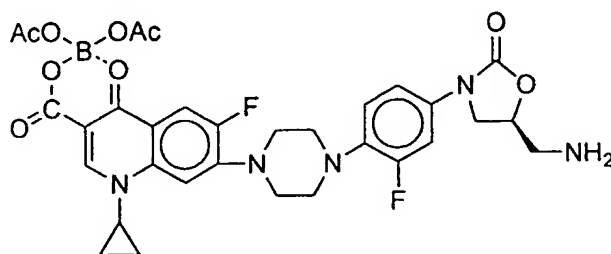
$^1\text{H}$ -RMN (DSMO- $\text{d}_6$ , 200 MHz,  $\delta$  (ppm)): 8,94 (s, 1H); 8,30 (t, 1H); 7,90 (d, 1H); 7,60-7,40 (m, 2H); 7,30-7,10 (m, 2H); 4,75 (m, 1H); 4,30-3,40 (m, 10H); 2,80 (s, 3H); 2,10-1.05 (m, 10H); 1.93 (s, 6H); 1.88 (s, 3H).

5

Reference Example No.33.

7-{4-[4-(5-(S)-aminomethyl-2-oxo-oxazolidin-3-yl)-2-fluoro-phenyl]-piperazin-1-yl}-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid  
 10 diacethoxyboron chelate.

15



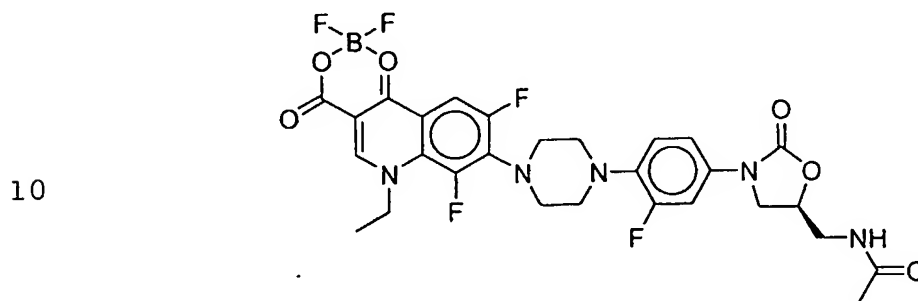
20 Following the procedure described in Reference Example No. 31 and using the product obtained in Reference Example No. 29 and using 2 equivalents of triethylamine instead of only one equivalent, the product of the title is obtained.

25  $^1\text{H}$ -RMN (DSMO- $\text{d}_6$ , 200 MHz,  $\delta$  (ppm)): 9,03 (s, 1H); 8,04 (d, 1H); 7,82 (d, 1H); 7,59 (dd, 1H); 7,24 (dd, 1H); 7,17 (t, 1H); 4,70-4,56 (m, 1H); 4,14 (s.a., 1H); 4,08 (t, 1H); 3,84 (dd, 1H); 3,64 (s.a., 4H); 3,23 (s.a., 4H); 2,90-2,70 (s.c., 2H); 2,20 (s.a., 2H,  $\text{NH}_2$ ); 1.90 (s, 6H);  
 30 1.50-1.20 (s.c., 4H).



## Reference Example No.34.

7-(4-{5-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid boron difluoride chelate.

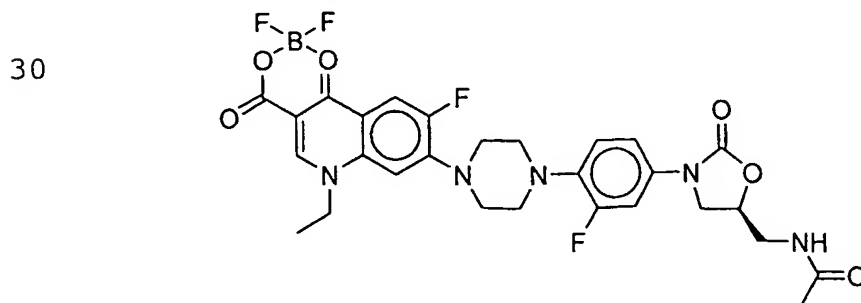


Following a procedure analogous to that described in Reference Example No. 31 and using 1-ethyl-6,7,8-trifluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid boron difluoride chelate (obtained according to WO 8807998) the product of the title is obtained.

$^1\text{H}$ -RMN (DSMO- $\text{d}_6$ , 200 MHz,  $\delta$  (ppm)): 9,44 (s, 1H); 8,27 (t, 1H, NH); 8,09 (d, 1H); 7,54 (dd, 1H); 7,30-7,06 (s.c., 2H); 5,00-4,60 (s.c., 3H); 4,10 (t, 1H); 3,80-2,95 (s.c., 11H); 1.85 (s, 3H); 1.55 (t, 3H).

## Reference Example No.35.

25 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid boron difluoride chelate.

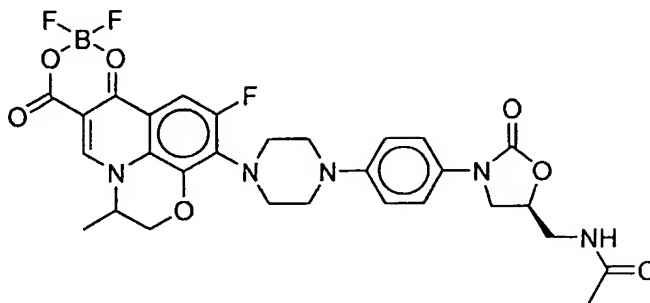


Following a procedure analogous to that described in Reference Example No. 31 and using 7-chloro-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid boron difluoride chelate (obtained according to JP 59122470) the product of the title is obtained.

$^1\text{H}$ -RMN (DSMO- $\text{d}_6$ , 200 MHz,  $\delta$  (ppm)): 9,42 (s, 1H); 8,30 (t, 1H, NH); 8,17 (d, 1H); 7,60-7,40 (s.c., 2H); 7,25-7,05 (s.c., 2H); 4,90 (c, 2H); 4,80-4,60 (m, 1H); 4,14 (t, 1H); 3,80-2,90 (s.c., 11H); 1.84 (s, 3H); 1.52 (t, 3H).

#### Reference Example No.36.

9-(4-{4-[5-(S)-(acetyl-amino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3-aza-phenalen-5-carboxylic acid boron difluoride chelate.



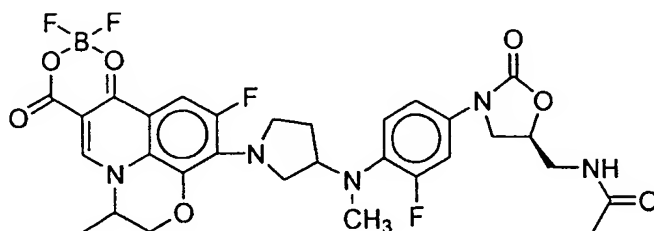
Using 8,9-difluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid boron difluoride chelate (obtained according to JP 58029789) and following a procedure analogous to that described in Reference Example No.31 the product of the title is obtained.

$^1\text{H}$ -RMN (DSMO- $\text{d}_6$ , 200 MHz,  $\delta$  (ppm)): 9,44 (s, 1H); 8,30 (t, 1H, NH); 7,84 (d, 1H); 7,43 (d, 2H); 7,05 (d, 2H); 5,30-5,10 (m, 1H); 4,80-4,30 (s.c., 3H); 4,10 (t, 1H); 3,80-3,15 (s.c., 11H); 1.84 (s, 3H); 1.58 (d, 3H).

## Reference Example No.37.

9-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluorophenyl}-methyl-amino)-pyrrolidone-1-yl]-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-  
phenalen-5-carboxylic acid boron difluoride chelate.

10



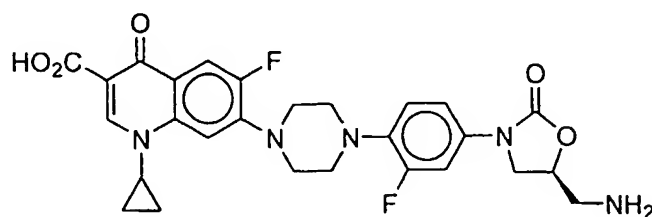
In a manner analogous to the previous example and using  
 15 the compound obtained in Reference Example No.27 the  
 product of the title is obtained.

<sup>1</sup>H-RMN (DSMO-d<sub>6</sub>, 200 MHz, δ (ppm)): 9,36 (s, 1H);  
 8,25 (t, 1H, NH); 7,74 (d, 1H); 7,50 (dd, 1H); 7,30-7,10  
 20 (s.c., 2H); 5,20-3,00 (s.c., 13H); 2,78 (s, 3H); 1.82 (s,  
 3H); 2,20-1.80 (s.c., 2H); 1.50 (d, 3H).

## Reference Example No.38.

4-{4-[4(5-(S)-aminomethyl-2-oxo-oxazolidin-3-yl)-2-fluoro-  
 25 phenyl]-piperazin-1-yl}-1-cyclopropyl-6-fluoro-4-oxo-1,4-  
dihydro-quinoline-3-carboxylic acid.

30



*Method 1:*

To 13.3 g (0.02 mol) of the product obtained in Reference  
5 Example No.33 in 300 ml of acetonitrile and 300 ml of  
water is added 96 ml (0.096 mol) of sodium hydroxide 1N.

It is stirred at room temperature for 2 h. The  
acetonitrile is concentrated in a rotovapor and to the  
10 resulting aqueous solution is added 96 ml of hydrochloric  
acid 1 N.

The precipitate formed is filtered to yield 2.8 g. The  
filtering liquids are extracted with 4 x 200 ml of  
15 dichloromethane/ethanol 90/10. The extracts are dried and  
and concentrated, thus yielding a further 6.8 g of the  
product of the title.

$^1\text{H}$ -RMN (DSMO- $\text{d}_6$ , 200 MHz,  $\delta$  (ppm)): 8,70 (s, 1H);  
20 7,95 (d, 1H); 7,63 (d, 1H); 7,58 (dd, 1H); 7,26-7,10  
(s.c., 2H); 4,80-4,60 (m, 1H); 4,08 (t, 1H); 3,96-3,80  
(s.c., 2H); 3,50 (s.a., 4H +  $\text{NH}_2$ ); 3,23 (s.a., 4H); 3,00-  
2,80 (s.c., 2H); 1.42-1.15 (s.c., 4H).

25 *Method 2:*

To 40 mg of the product obtained by method 1 of Reference  
Example No.5, dissolved in 10 ml of ethanol, is added 0.10  
mg of 10% Pd/C paste, and it is placed under atmosphere of  
30 hydrogen at atmospheric pressure and room temperature. When  
the reaction finishes it is filtered over decalite, which  
is washed with 2 x 10 ml of ethanol.

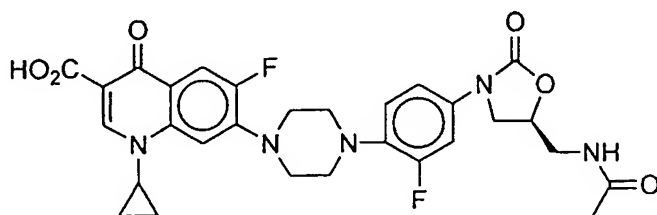
The filtering liquids are concentrated to dryness and thus yield 20 mg of a product identical to that obtained by method 1.

5                    **COMPOUNDS OF GENERAL FORMULA (I)**

**Example 1:**

7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-  
10 fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

15



20

To 0.8 g (1.13 mol) of the product of Reference Example No.31 in 20 ml of water and 20 ml of acetonitrile is added 5.6 ml of sodium hydroxyde 1N, and it is stirred at room temperature for 1 h.

The acetonitrile is concentrated and the aqueous phase is acidified with 5.6 ml of hydrochloric acid 1N.

It is extracted with 3 x 50 ml of dichloromethane/ethanol 9/1.

25

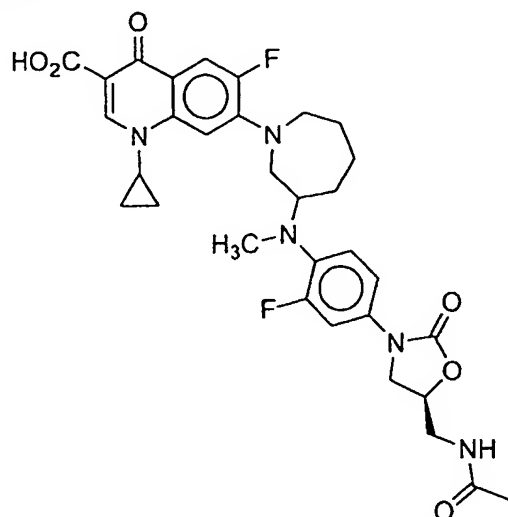
The organic phase is dried and concentrated. The residue is stirred for 10 min with 2-propanol and the precipitated solid is filtered. Thus are obtained 290 mg of the product of the title.

30

<sup>1</sup>H-RMN (DSMO-d<sub>6</sub>, 200 MHz, δ (ppm)): 8,72 (s, 1H); 8,33 (t, 1H, NH); 7,99 (d, 1H); 7,64 (d, 1H); 7,58 (dd, 1H); 7,30-7,10 (s.c., 2H); 4,84-4,64 (m, 1H); 4,16 (t, 1H); 3,90-2,90 (s.c., 12H); 1,90 (s, 3H); 1,44-1,16 (s.c., 4H).

**Example 2:**

7-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-azepan-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

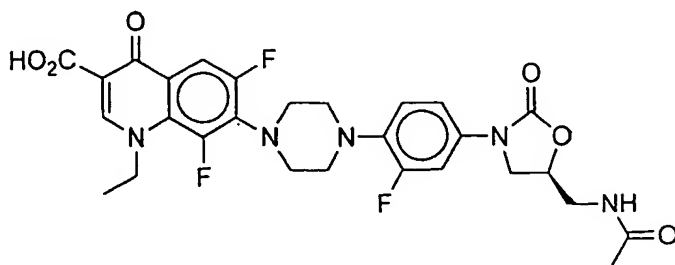


It is obtained by following the procedure of Example 1 and using the product obtained in Reference Example No.32.

$^1\text{H}$ -RMN (DSMO- $d_6$ , 200 MHz,  $\delta$  (ppm)): 8,59 (s, 1H); 8,30 (t, 1H, NH); 7,80 (d, 1H); 7,50 (dd, 1H); 7,30 (d, 1H); 7,25-7,05 (s.c., 2H); 4,75 (m, 1H); 4,20-3,20 (m, 10H); 2,76 (s, 3H); 2,20-1.00 (m, 10H); 1.86 (s, 3H).

**Example 3:**

7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



To 1.9 g (3mmol) of the product obtained in Reference Example No.34 in 100 ml of ethanol and 2.5 ml of water is added 10 ml of triethylamine, and it is heated to reflux 5 for 16 h.

The precipitated salts are filtered. The filtering liquids are concentrated to dryness and the residue is treated with 50 ml of water and the pH adjusted to 5 by addition 10 of hydrochloric acid 1N.

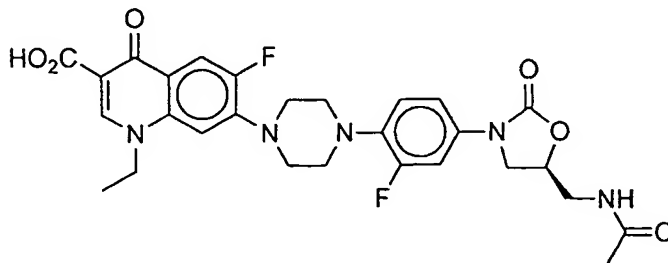
It is extracted with 3 x 75 ml of dichloromethane/ethanol 9/1. The organic phase is dried and concentrated. Thus are obtained 1.2 g of a white solid.

15  $^1\text{H}$ -RMN (DSMO- $\text{d}_6$ , 200 MHz,  $\delta$  (ppm)): 8,94 (s, 1H); 8,30 (t, 1H, NH); 7,87 (d, 1H); 7,50 (dd, 1H); 7,25-7,02 (s.c., 2H); 4,80-4,30 (s.c., 3H); 4,10 (t, 1H); 3,80-3,20 (s.c., 7H); 3,10 (s.a., 4H); 1,82 (s, 3H); 1,42 (t, 3H).

#### 20 Example 4:

7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

25



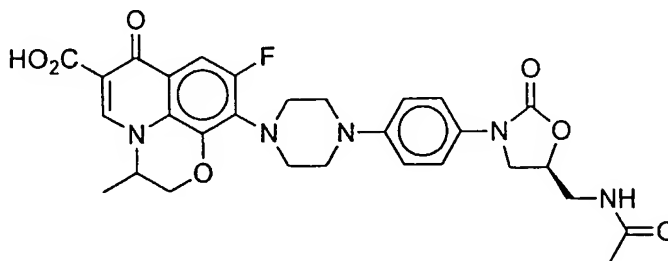
30

Following the procedure of the previous example and using the product obtained in Reference Example No.35 the product of the title is achieved.

5  $^1\text{H}$ -RMN (DSMO- $\text{d}_6$ , 200 MHz,  $\delta$  (ppm)): 8,99 (s, 1H); 8,30 (t, 1H, NH); 7,96 (d, 1H); 7,54 (d, 1H); 7,20-7,05 (s.c., 3H); 5,00-4,56 (s.c., 3H); 4,14 (t, 1H); 3,90-3,10 (s.c., 11H); 1.82 (s, 3H); 1,60-1,35 (s.a., 3H).

10 **Example 5:**

9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid



15

Following the procedure described in Example 3 and using the product obtained in Reference Example No.36 the product of the title is achieved.

20  $^1\text{H}$ -RMN (DSMO- $\text{d}_6$ , 200 MHz,  $\delta$  (ppm)): 9,00 (s, 1H); 8,26 (t, 1H, NH); 7,62 (d, 1H); 7,41 (d, 2H); 7,02 (d, 2H); 5,05-4,90 (m, 1H); 4,80-4,75 (s.c., 2H); 4,41 (d, 1H); 4,10 (t, 1H); 3,80-3,00 (s.c., 11H); 1.84 (s, 3H); 1.46 (d, 3H).

25

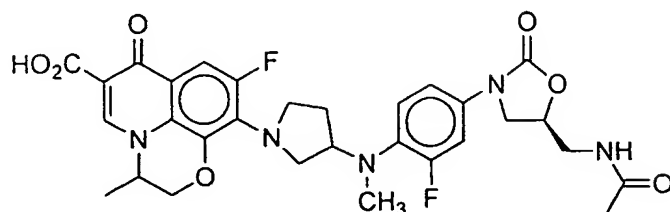
**Example 6:**

9-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-



fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid

5



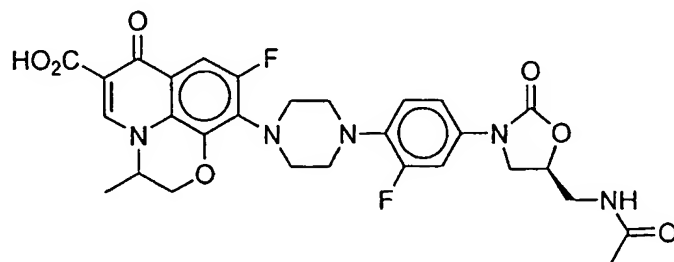
10 Following the procedure of Example No.3 and using the product of Reference Example No.37 the product of the title is obtained.

$^1\text{H}$ -RMN (DSMO- $d_6$ , 200 MHz,  $\delta$  (ppm)): 8,92 (s, 1H);  
 15 8,30 (t, 1H, NH); 7,60-7,40 (s.c., 2H); 7,30-7,10 (s.c., 2H); 4,95-4,80 (m, 1H); 4,80-4,45 (s.c., 3H); 4,40-4,20 (s.c., 1H); 4,10 (t, 1H), 4,02-3,20 (s.c., 7H); 2,70 (s, 3H); 2,20-1.90 (s.c., 2H); 1,84 (s, 3H); 1,45 (s.a., 3H).

## 20 Example 7:

9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid

25



30

To 1.6 g (5mmol) of 8,9-difluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid boron difluoride chelate and 1.7 g (5mmol) of N-[3-(3-Fluoro-4-piperazin-1-yl-phenyl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-

acetamide (obtained according to US 5547950) in 50 ml of N-methyl-pyrrolidin-2-one is added 0.7 ml (5mmol) of triethylamine and it is heated at 110°C for 16 h.

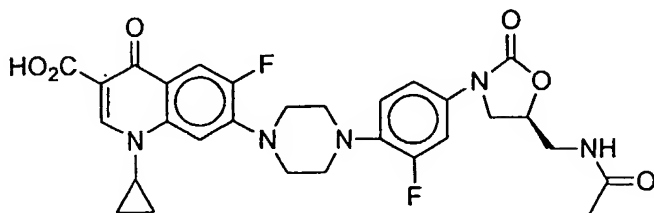
5 The solvent is distilled under vacuum and the residue is stirred for 30 min with dichloromethane/ethanol, precipitating a solid which is filtered and yields 1.2 g (40%) of pure product.

<sup>1</sup>H-RMN (DSMO-d<sub>6</sub>, 200 MHz, δ (ppm)): 9,00 (s, 1H);  
10 8,25 (t, 1H, NH); 7,62 (d, 1H); 7,52 (dd, 1H); 7,30-7,10 (s.c., 2H); 4,99 (m, 1H); 4,80-4,60 (m, 1H); 4,62 (d, 1H); 4,40 (d, 1H); 4,10 (t, 1H); 3,80-3,60 (m, 1H); 3,60-2,80 (s.c., 10H); 1,84 (s, 3H); 1,50 (d, 3H).

#### 15 Example 8:

7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

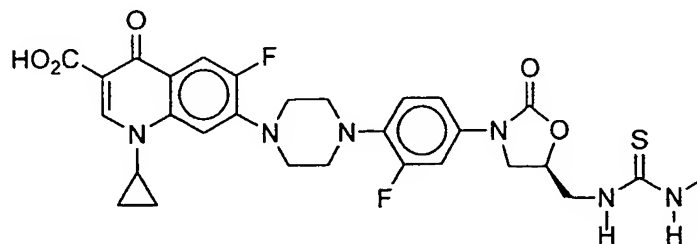
20



25 To 6 g (0.011 mol) of the product of Reference Example No.38 in 100 ml of pyridine is added 2.8 ml (0.022 mol) of acetic anhydride. It is heated at 50°C for 2 h. The pyridine is concentrated to dryness and to the residue is added 200 ml of water and it is stirred for 5 min. The  
30 precipitated solid is filtered and dissolved in dichloromethane and chromatographed on silica gel. Elution with dichloromethane-ethanol 90/10 yields 4 g (63%) of pure product identical to that obtained in Example 1.

**Example 9:**

1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methylthioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



10

To 0.81 g (1.5 mmol) of the product of Reference Example No.38 in 10 ml of pyridine is added 0.22 g (3 mmol) of methylisothiocyanate. It is heated at 60°C for 10 minutes. It is concentrated to dryness and the residue is stirred for 20 min with 30 ml of water. The precipitated solid is filtered and 0.5 g of pure product is obtained.

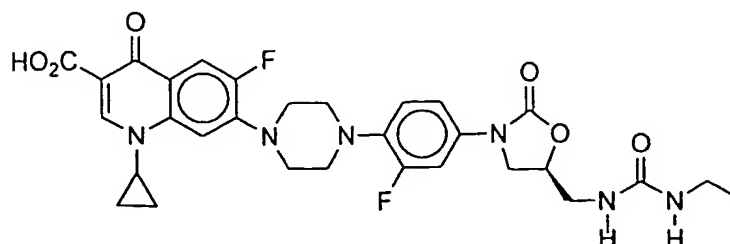
<sup>1</sup>H-RMN (DSMO-d<sub>6</sub>, 200 MHz, δ (ppm)): 8,70 (s, 1H); 7,98 (d, 1H); 7,82 (t, 1H, NH); 7,80-7,50 (s.a., 1H, NH); 7,64 (d, 1H); 7,56 (dd, 1H); 7,30-7,10 (s.c., 2H); 4,95-4,80 (m, 1H); 4,16 (t, 1H); 4,00-3,70 (s.a., 4H); 3,60-3,40 (s.a., 4H); 3,30-3,10 (s.a., 4H); 2,82 (s.a., 3H); 1.44 -1.16 (s.c., 4H).

25

**Example 10:**

1-cyclopropyl-7-[4-(4-{5-(S)-[(3-ethyl-ureido)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

30



In a similar way to the previous Example and replacing the methylisothiocyanate by ethylisocyanate the product of the title is obtained.

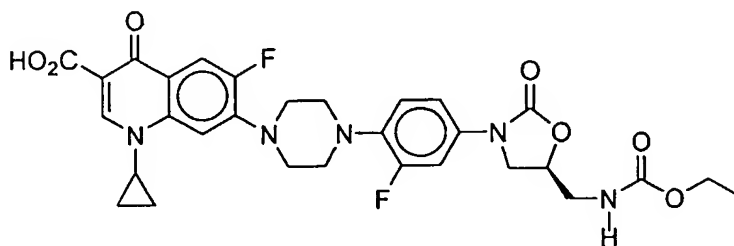
5

$^1\text{H}$ -RMN (DSMO- $\text{d}_6$ , 200 MHz,  $\delta$  (ppm)): 8,70 (s, 1H); 7,96 (d, 1H); 7,66 (d, 1H); 7,58 (dd, 1H); 7,30-7,10 (s.c., 1H); 6,22 (t, 1H, NH); 5,99 (t, 1H, NH); 4,80-4,64 (s.c., 1H); 4,10 (t, 1H); 3,90-3,78 (m, 1H); 3,72 (dd, 10 1H); 3,60-3,20 (s.c., 10H); 3,10-2,90 (s.c., 2H); 1.44-1.10 (s.c., 4H); 0.98 (t, 3H).

**Example 11:**

1-cyclopropyl-7-(4-{4-[5-(S)-(ethoxycarbonylamino-methyl)-15 2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

20



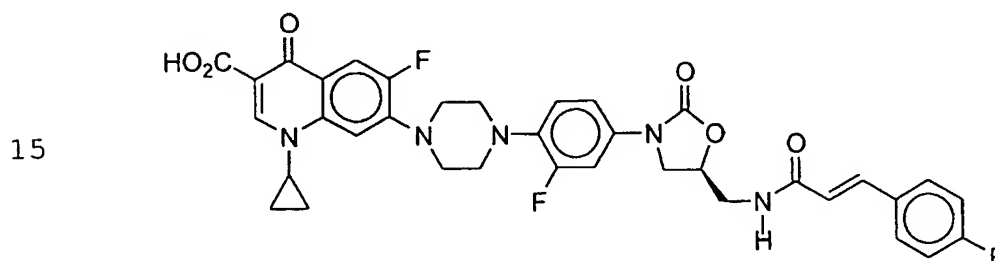
To 0.81 g of the product of Reference Example 25 No.38 in 20 ml of tetrahydrofuran are added 0.25 g of sodium bicarbonate and 0.3 g of ethyl chloroformate.

It is heated to reflux for 16 h. It is concentrated to dryness and the residue is treated with 30 ml of water and extracted with 3 x 50 ml of dichloromethane-ethanol 90/10. The organic phase is dried and concentrated to a volume of 20 ml. The precipitated solid is filtered and 0.3 g of pure product is obtained.

$^1\text{H}$ -RMN (DSMO- $d_6$ , 200 MHz,  $\delta$  (ppm)): 8,70 (s, 1H); 7,98 (d, 1H); 7,64 (d, 1H); 7,56 (dd, 1H); 7,50 (t, 1H, NH); 7,30-7,10 (s.c., 2H); 4,80-4,64 (m, 1H); 4,14 (t, 1H); 4,02 (c, 2H); 3,96-3,70 (s.c., 2H); 3,60-3,10 (s.c., 5 10H); 1.42-1.10 (s.c., 4H); 1.17 (t, 3H).

**Example 12:**

1-cyclopropyl-6-fluoro-7-{4-[2-fluoro-4-(5-(S)-{[3-(4-fluoro-phenyl)-acryloylamino]-methyl}-2-oxo-oxazolidin-3-  
10 yl)-phenyl]-piperazin-1-yl}-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



To 0.6 g (1.1 mmol) of the product of Reference  
20 Example No.38 in 20 ml of dry dichloromethane are added  
0.17 ml (1.22 mmol) of triethylamine and 0.3 g (1.33 mmol)  
of 4-fluorocinnamoyl chloride.

The reaction is maintained at room temperature for  
25 16 h, then concentrated to dryness and the residue is  
chromatographed on silica gel.

Elution with dichloromethane-ethanol 95/5 yields  
0.3 g of pure product.

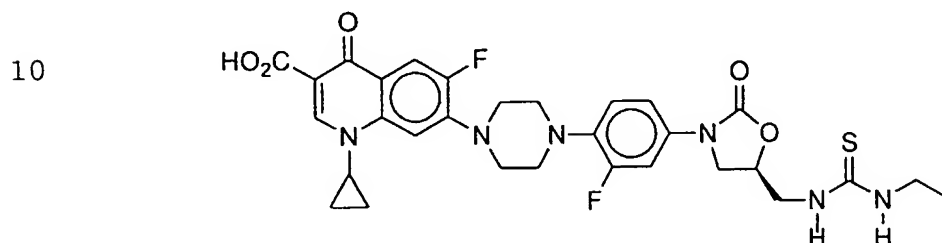
30

$^1\text{H}$ -RMN (DSMO- $d_6$ , 200 MHz,  $\delta$  (ppm)): 8,70 (s, 1H);  
8,58 (t, 1H, NH); 7,96 (d, 1H); 7,70-7,58 (s.c., 4H); 7,44  
(d, 1H); 7,30-7,10 (s.c., 4H); 6,64 (d, 1H); 4,90-4,76 (m,

1H); 4,16 (t, 1H); 3,92-3,70 (s.c., 2H); 3,64-3,10 (s.c., 10H); 1.42-1.10 (s.c., 4H).

### Example 13:

5 1-cyclopropyl-7-[4-(4-{5-(S)-[(3-ethylthioureido)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluorophenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

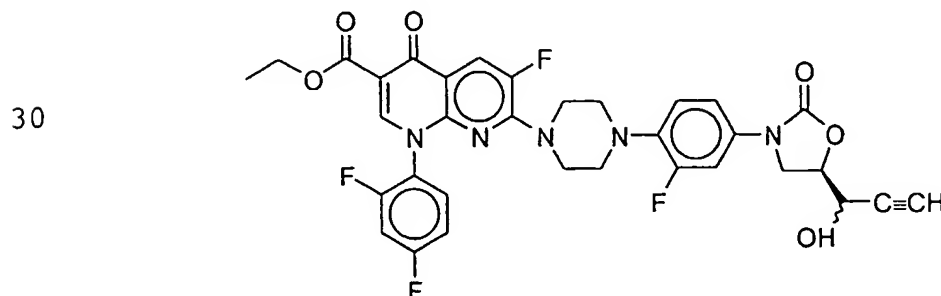


15 Following the procedure described in Example No. 9, replacing the methylisothiocyanate by ethylisothiocyanate, the product of the title is obtained.

<sup>1</sup>H-RMN (DSMO-d<sub>6</sub>, 200 MHz, δ (ppm)): 15,06 (s.a., 1H); 8,70 (s, 1H); 7,98-7,50 (m, 4H); 7,30-7,10 (s.c., 20 2H); 4,95-4,80 (m, 1H); 4,16 (t, 1H); 4,00-3,70 (s.a., 4H); 3,60-3,10 (m., 10H); 1.44 -1.16 (s.c., 4H).; 1.02 (t., 3H).

### Example 14

1-(2,4-difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-5-[5-(R)-  
25 (1-(R,S)-hydroxy-prop-2-ynyl)-2-oxo-oxazolidin-3-yl]-phenyl}piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester



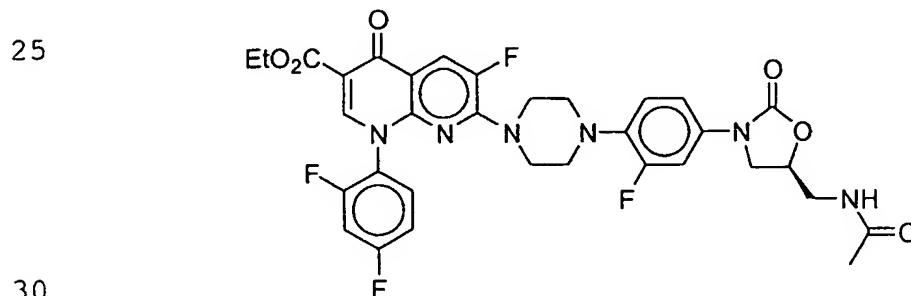
To 0.32 g (1 mmol) of the product of Reference Example No.30 in 10 ml of pyridine are added 0.42 g (1mmol) of 7-chloro-1-(2,4-difluorophenyl)-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester (ACROS) and 0.28 ml of triethylamine. The reaction is maintained at room temperature for 48 h. It is concentrated to dryness and the residue is chromatographed on silica gel.

10 Elution with dichloromethane/ethanol/ammonium hydroxide 95/5/1% yields 0.436 g (66%) of the product of the title.

<sup>1</sup>H-RMN (CDCl<sub>3</sub>, 200 MHz, δ (ppm)): 8,42 (s, 1H); 15 8,15 (d, 1H); 7,40 (m, 2H); 7,10 (m, 3H); 6,90 (t, 1H); 4,75 (m, 1H); 4,70 (m, 1H); 4,38 (c, 2H); 4,10 (m, 2H); 3,70 (m, 4H); 3,04 (m, 4H); 2,50 (m, 1H); 1.40 (t, 3H).

#### Example 15

20 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid ethyl ester.



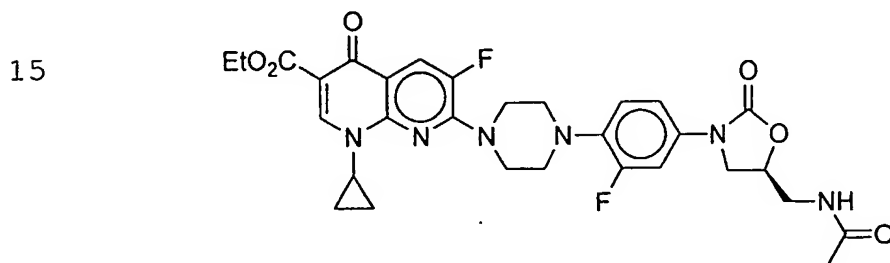
Following the procedure of the previous example and using N-[3-(3-Fluoro-4-piperazin-1-yl-phenyl)-2-oxo-

oxazolidin-5-(S)-ylmethyl]-acetamide (obtained according to US 5547950) the product of the title is obtained.

<sup>1</sup>H-RMN (CDCl<sub>3</sub>, 200 MHz, δ (ppm)): 8,41 (s, 1H); 8,15 (d, 1H); 7,42 (dd, 1H); 7,16-6,80 (s.c., 5H); 6,41 (t, 1H, NH); 4,84-4,70 (m, 1H); 4,39 (c, 2H); 4,02 (t, 1H); 4,80-4,60 (s.c., 7H); 3,10-2,95 (s.a., 4H); 2,02 (s, 3H); 1.40 (t, 3H).

### Example 16

10 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid ethyl ester



20 Following the procedure described in example 14 and using N-[3-(3-Fluoro-4-piperazin-1-yl-phenyl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide (obtained according to US 5547950) and 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid ethyl  
25 ester (EP 0187376B1) the product of the title is obtained.

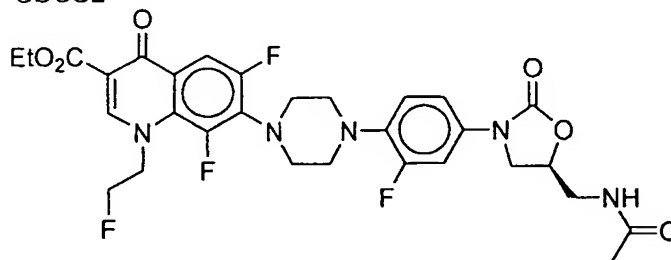
<sup>1</sup>H-RMN (CDCl<sub>3</sub>, 200 MHz, δ (ppm)): 8,52 (s, 1H); 8,11 (d, 1H); 7,48 (dd, 1H); 7,08 (m, 1H); 6,94 (t, 1H); 6,74 (t, 1H, NH); 4,79 (m, 1H); 4,37 (c, 2H); 4,01 (m, 30 5H); 3,76 (m, 1H); 3,66 (m, 2H); 3,53 (m, 1H); 3,20 (m, 4H); 2,04 (s, 3H); 1.40 (t, 3H); 1.23 (m, 2H); 1.05 (m, 2H).



**Example 17**

7-(4-{4-[5-(S)-(acetyl-amino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6,8-difluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester

10

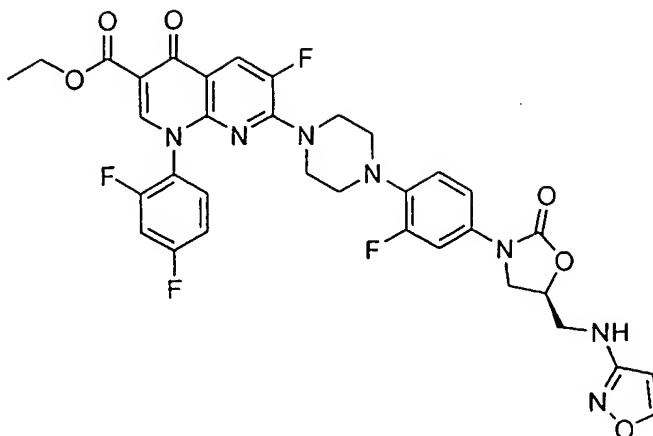


Following a procedure analogous to the previous ones and replacing the derivative of naphthyridine by 6,7,8-trifluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester, the product of the title is obtained.

$^1\text{H}$ -RMN (DMSO- $d_6$ , 200 MHz,  $\delta$  (ppm)): 8,59 (s, 1H); 8,30 (t, 1H, NH); 7,79 (d, 1H); 7,50 (d, 1H); 7,30-7,00 (s.c., 2H); 5,05-4,60 (s.c., 5H); 4,21 (c, 2H); 4,15 (t, 1H); 3,80-3,00 (s.c., 11H); 1.82 (s, 3H); 1.27 (t, 3H).

**Example 18**

1-(2,4-Difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-(S)-(isoxazol-3-ylaminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester.



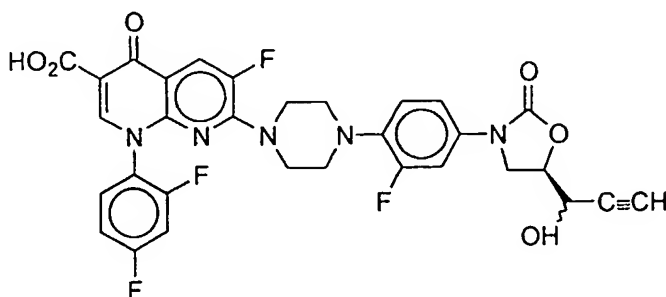
Following the procedure of example 14 and replacing the product of Reference Example No.30 by the product of Reference Example No.25 1-(2,4-difluoro-5 phenyl)-6-fluoro-7-{4-[2-fluoro-4-(5-(R)-{isoxazol-3-yl-(2,2,2-trichloro-ethoxycarbonyl)-amino}-methyl)-2-oxo-oxazolidin-3-yl]-phenyl]-piperazin-1-yl}-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester is obtained. To 500 mg thereof, dissolved in 10 ml of tetrahydrofuran is added 5 ml of water, 5 ml of glacial acetic acid and 700 mg of powdered zinc. After stirring for 3 h at room temperature it is filtered over decalite and the filtering liquids concentrated and chromatographed on silica gel. Elution with dichloromethane/ethanol/ammonium hydroxide 98/2/02% yields 247 mg of the product of the title.

$^1\text{H}$ -RMN ( $\text{CDCl}_3$ , 200 MHz,  $\delta$  (ppm)): 8,41 (s, 1H); 8,15 (d, 1H); 8,07 (d, 1H); 7,45 (m, 2H); 7,05 (m, 3H); 6,85 (t, 1H); 5,85 (s, 1H); 4,95 (m, 1H); 4,50 (m, 1H); 4,38 (c, 2H); 4,05 (t, 1H); 3,80 (m, 2H); 3,68 (m, 4H); 3,03 (m, 4H); 1.39 (t, 3H).

**Example 19**

1-(2,4-difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-(R)-(1-hydroxy-prop-2-ynyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-  
5 carboxylic acid

10



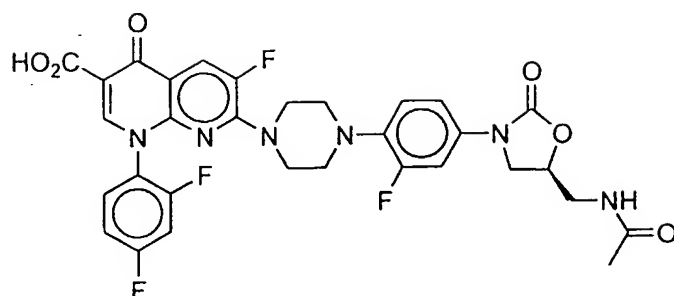
To 0.436 g (0.6 mmol) of the product of example 14  
15 in 5 ml of ethanol and 5 ml of water is added 1.32 ml of  
sodium hydroxyde 1N. It is heated at 50°C for 3 h. 1.32 ml  
of HCl 1N is added and it is concentrated to dryness. The  
residue is chromatographed on silica gel. Elution with  
dichloromethane/ethanol/acetic acid 95/5/0.5% yields 0.287  
20 g (75%) of the product of the title.

<sup>1</sup>H-RMN (CDCl<sub>3</sub>, 200 MHz, δ (ppm)): 8,68 (s, 1H);  
8,15 (d, 1H); 7,60-7,27 (m, 2H); 7,20-7,00 (m, 3H); 6,90  
(t, 1H); 4,75 (m, 1H); 4,30-4,00 (m, 2H); 3,80 (m, 4H);  
25 3,28 (dd, 1H); 3,20 (m, 1H); 2,50 (d, 1H).

**Example 20**

7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-  
yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-(2,4-difluoro-  
30 phenyl)-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-  
carboxylic acid

5



10           Following the procedure described in the previous  
example and using the product described in Example No.15  
the product of the title is obtained.

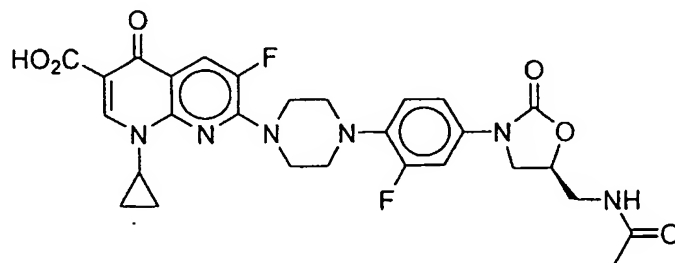
$^1\text{H}$ -RMN (DMSO- $d_6$ , 200 MHz,  $\delta$  (ppm)): 8,90 (s, 1H),  
15 8,27 (t, 1H); 8,22 (d, 1H); 7,95-7,80 (m, 1H); 7,80-7,60  
(m, 1H); 7,50 (d, 1H); 7,45-7,30 (m, 1H); 7,25-7,00 (s.c.,  
2H); 4,80-4,62 (m, 1H); 4,12 (t, 1H); 3,80-2,95 (s.c.,  
11H); 1.84 (s, 3H).

20

**Example 21**

7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-  
yl]-2-fluorophenyl}-piperazin-1-yl)-1-cyclopropyl-6-  
fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic  
acid

25



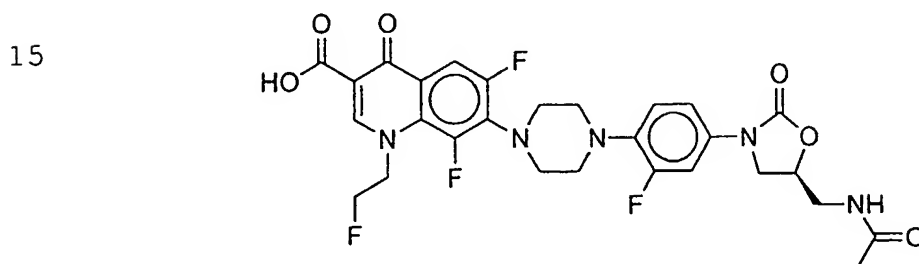
30

From the product of Example No.16 and following  
the procedure described above the product of the title is  
obtained.

$^1\text{H}$ -RMN ( $\text{CDCl}_3$ , 200 MHz,  $\delta$  (ppm)): 8,74 (s, 1H); 8,12 (m, 1H); 8,10 (d, 1H); 7,50 (m, 1H); 7,12 (m, 1H); 6,95 (t, 1H); 4,79 (m, 1H); 4,10 (m, 4H); 4,05 (m, 1H); 3,89 (m, 1H); 3,67 (m, 1H); 3,58 (m, 2H); 3,24 (m, 4H); 2,00 (s, 3H); 1.30 (m, 2H); 1.15 (m, 2H).

### Example 22

7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6,8-difluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



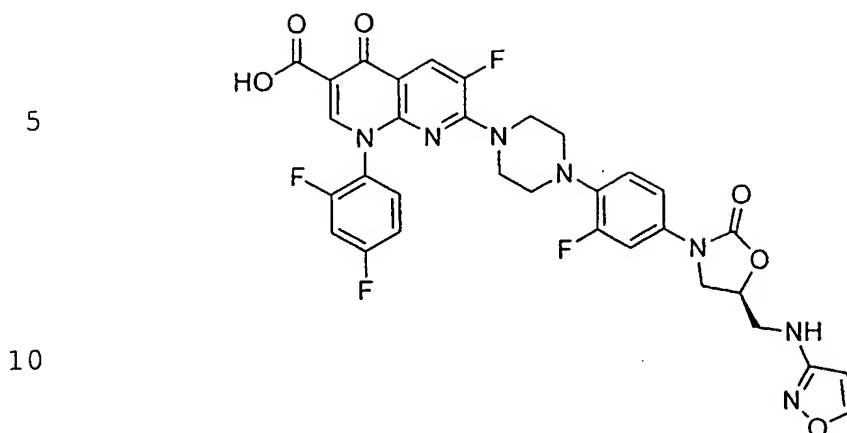
From the product of Example No.17 and following the procedure described in Example No.19, the product of the title is obtained.

25  $^1\text{H}$ -RMN ( $\text{DMSO}-d_6$ , 200 MHz,  $\delta$  (ppm)): 8,84 (s, 1H); 8,26 (t, 1H, NH); 7,92 (d, 1H); 7,56 (d, 1H); 7,35 -7,05 (s.c., 2H); 5,16-4,64 (s.c., 5H); 4,12 (t, 1H); 3,80-3,00 (s.c., 11H); 1.82 (s, 3H).

### 30 Example 23

1-(2,4-Difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-(S)-(isoxazol-3-ylaminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid

35



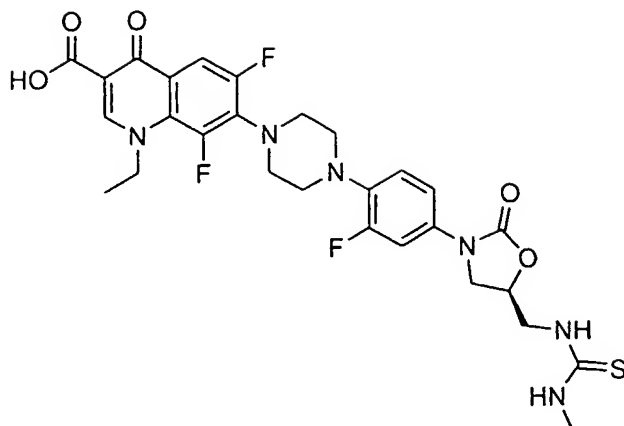
From the product of Example No.18 and following procedure described in Example No.19, the product of the title is 15 obtained.

$^1\text{H}$ -RMN ( $\text{CDCl}_3$ , 200 MHz,  $\delta$  (ppm)): 8,69 (s, 1H); 8,15 (d, 1H); 8,06 (d, 1H); 7,45 (m, 2H); 7,10 (m, 3H); 6,90 (t, 1H); 5,90 (s, 1H); 4,95 (m, 1H); 4,50 (m, 1H); 20 4,06 (t, 1H); 4,00-3,50 (m, 6H); 3,05 (m, 4H).

#### Example 24

1-ethyl-6,8-difluoro-7-[4-(2-fluoro-4-{5-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

25



To 2 g (6,7 mmol) of 1-ethyl-6,7,8-trifluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester in 5 40 ml of N-methyl-2-pyrrolidone are added 3.1 g (6.7 mmol) of the product of Reference Example No.33 and 1.85 ml of triethylamine. The reaction is heated at 100°C for 48 h.

The solvent is distilled under vacuum and the residue is 10 chromatographed on silica gel. Elution with dichloromethane/ethanol 90/10 yields 7-{4-[4-(5-(S)-aminomethyl-2-oxo-oxazolidin-3-yl)-2-fluoro-phenyl]-piperazin-1-yl}-1-ethyl-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester. From said product 15 and by following procedure described in Example No.19, the product of the title is obtained.

IR: 3380  $\text{cm}^{-1}$  1750  $\text{cm}^{-1}$  1620  $\text{cm}^{-1}$  1510  $\text{cm}^{-1}$

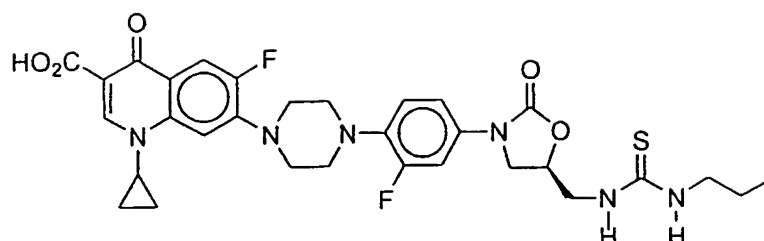
20

### Example 25

1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{2-oxo-5-(S)-[(3-propyl-thioureido)-methyl]-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic

25 acid

5



10 Following the procedure described in Example No. 9,  
 replacing the methylisothiocyanate by  
 propylisothiocyanate, the product of the title is  
 obtained.

$^1\text{H}$ -RMN (DSMO- $\text{d}_6$ , 200 MHz,  $\delta$  (ppm)): 8,70 (s, 1H);  
 15 7,92 (d., 1H), 7,90-7,70 (m, 2H, NH); 7,70-7,50 (m., 2H);  
 7,30-7,10 (m., 2H); 4,95-4,80 (m, 1H); 4,16 (t, 1H); 4,00-  
 3,70 (s.a., 4H); 3,60-3,10 (m., 10H); 1.60 -1.16 (s.c.,  
 6H).; 0.84 (t., 3H).

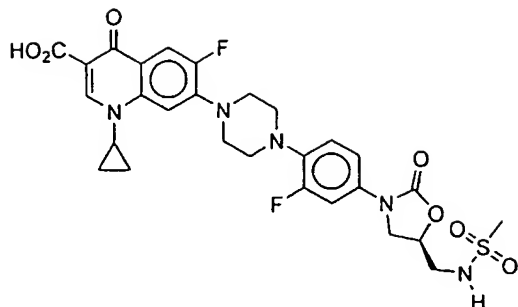
20

**Example 26**

1-cyclopropyl-6-fluoro-7-[4-{2-fluoro-4-[5-(S)-  
 (methanesulfonylamino-methyl)-2-oxo oxazolidin-3-yl]-  
 phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-3-  
 25 carboxylic acid



5



10 Following the procedure described in Example No. 9,  
replacing the methylisothiocyanate by  
methanesulphonylchloride, the product of the title is  
obtained.

15  $^1\text{H}$ -RMN (DSMO- $d_6$ , 200 MHz,  $\delta$  (ppm)): 15,00 (s.a.,  
1H); 8,70 (s, 1H); 7,96 (d., 1H), 7,76-7,42 (m, 3H); 7,30-  
7,10 (m., 2H); 4,90-4,76 (m, 1H); 4,18 (t, 1H); 4,00-3,20  
(m., 12H); 2,98 (s, 3H); 1.44 -1.16 (m., 4H).

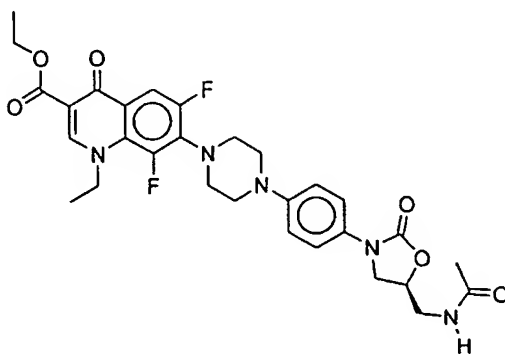
20

**Example 27**

7-(4-{4-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-  
yl]-phenyl}-piperazin-1-yl)-1-ethyl-6,8-fluoro-4-oxo-1,4-  
dihydro-quinoline-3-carboxylic acid ethyl ester

25

30



Following the procedure described in Example No. 14, using the product obtained in Reference Example No. 26 and 1-ethyl-6,7,8-trifluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (obtained by esterification of the corresponding acid, described in GB 2057440).

$^1\text{H}$ -RMN (DSMO- $\text{d}_6$ , 200 MHz,  $\delta$  (ppm)): 8,62 (s, 1H); 8,30 (t, 1H, NH); 7,80 (d., 1H), 7,42 (d, 2H); 7,04 (d., 2H); 4,84-4,64 (m, 1H); 4,60-4,40 (s.a., 2H); 4,26 (c, 2H); 4,16 (t, 1H); 3,78 (t, 1H); 3,60-3,20 (m., 10H); 1.90 (s, 3H); 1.44 (t, 3H); 1.30 (t., 3H).

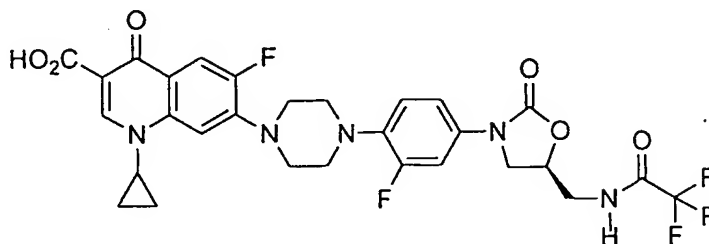
### Example 28

15

1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{2-oxo-5-(S)-[(2,2,2-trifluoro-acetyl-amino)-methyl]-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.

20

25

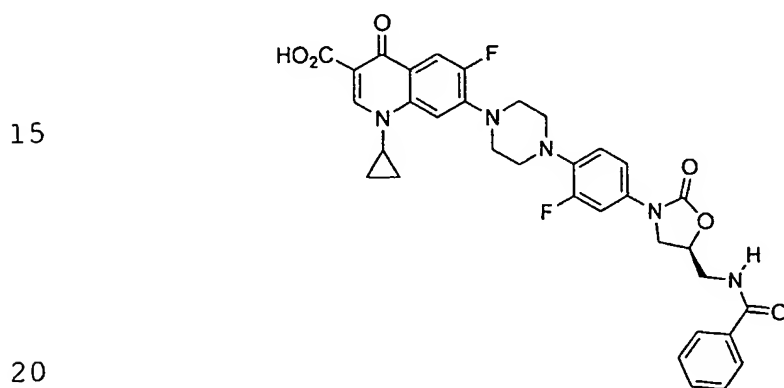


Following the procedure described in Example No. 9, replacing the methylisothiocyanate by trifluoroacetic anhydride, the product of the title is obtained.

<sup>1</sup>H-RMN (DSMO-d<sub>6</sub>, 200 MHz, δ (ppm)): 15,06 (s.a., 1H); 9,92 (s.a., 1H, NH); 8,70 (s, 1H); 7,95 (d, 1H,); 7,70-7,50 (m, 2H); 7,30-7,10 (s.c., 2H); 4,95-4,80 (m, 1H); 4,20 (t, 1H); 4,00-3,80 (s.a., 2H); 3,60-3,20 (m., 5 10H); 1.44 -1.16 (m., 4H).

### Example 29

7-(4-{4-[5-(S)-(benzoylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro 4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.



Following the procedure described in Example No. 9, replacing the methylisothiocyanate by benzoyl chloride, the product of the title is obtained.

25

<sup>1</sup>H-RMN (DSMO-d<sub>6</sub>, 200 MHz, δ (ppm)): 15,20 (s.a., 1H); 8,90 (t, 1H, NH); 8,70 (s, 1H); 8,00-7,85 (m., 3H), 7,76-7,42 (m, 5H); 7,30-7,10 (m., 2H); 4,96-4,80 (m, 1H); 4,20 (t, 1H); 4,00-3,20 (m., 12H); 1.44 -1.16 (m., 4H).

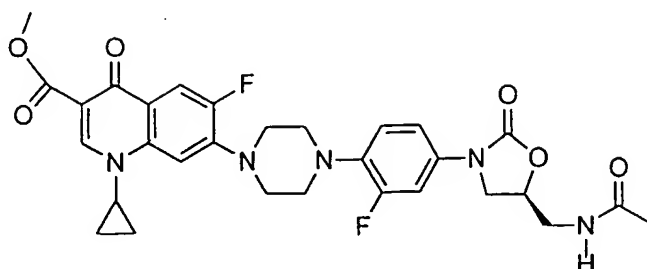
30

### Example 30

7-(4-{4-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-

fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid  
methyl ester.

5



To 1 g (1.7 mmol) of the product of Example 1 in 30 ml of  
10 methanol cooled to 0°C is added dropwise 0.37 ml (5.2  
mmol) of thionyl chloride. When the addition is finished  
it is heated to reflux for 48 hours. It is concentrated to  
dryness and the residue is chromatographed on silica gel.  
Elution with dichloromethane/methanol/acetic acid 90/10/1  
15 yields the product of the title as hydrochloride.

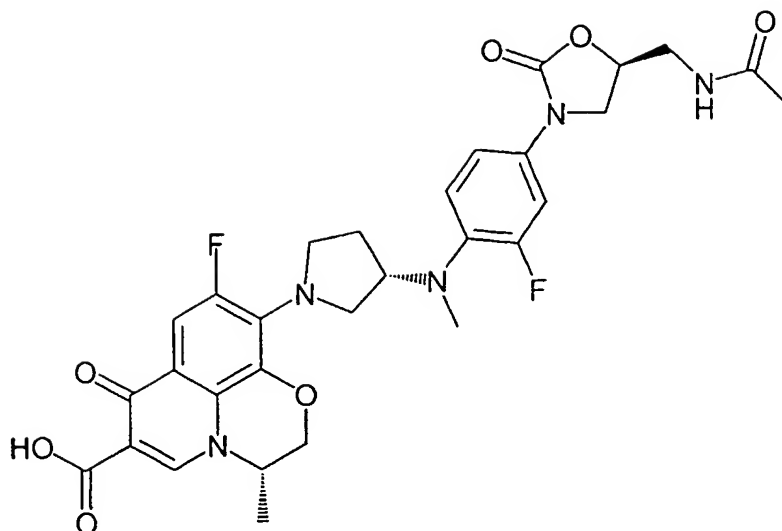
The product thus obtained is dissolved in  
dichloromethane/methanol 90/10 and washed with saturated  
solution of sodium bicarbonate. The organic phase is dried  
20 and concentrated to yield the product of the title in the  
form of free base.

<sup>1</sup>H-RMN (DSMO-d<sub>6</sub>, 200 MHz, δ (ppm)): 8,50 (s, 1H);  
8,25 (s.a., 1H, NH); 7,92 (d., 1H), 7,64-7,50 (m, 2H);  
25 7,30-7,10 (m., 2H); 4,90-4,70 (m, 1H); 4,16 (t, 1H); 3,90-  
3,60 (m., 5H); 3,60-3,20 (m., 10H); 1.86 (s., 1H); 1.45 -  
1.10 (m., 4H).

### EXAMPLE 31

30

9-[3-(S)-({4-[5-(S)-(Acetylamino-methyl)-2-oxo-  
oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-  
pyrrolidin-1-yl]-8-fluoro-3-(S)-methyl-6-oxo-2,3-dihydro-  
6H-1-oxa-3a-aza-phenalene-5-carboxylic acid.



Following the procedure described in Example 3 and starting  
 5 with the corresponding chelate obtained by reaction of N-  
 {3-(S)-[3-Fluoro-4-(methyl-pyrrolidin-3-yl-amino)-phenyl]-  
 2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide (obtained  
 following the procedure for the obtention of Reference  
 Example No.27, but replacing 3(R,S)-aminopyrrolidine by 3-  
 10 (S)-aminopyrrolidine) and 8,9-Difluoro-3-(S)-methyl-6-oxo-  
 2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid  
 boron difluoride chelate the product of the title is  
 obtained.

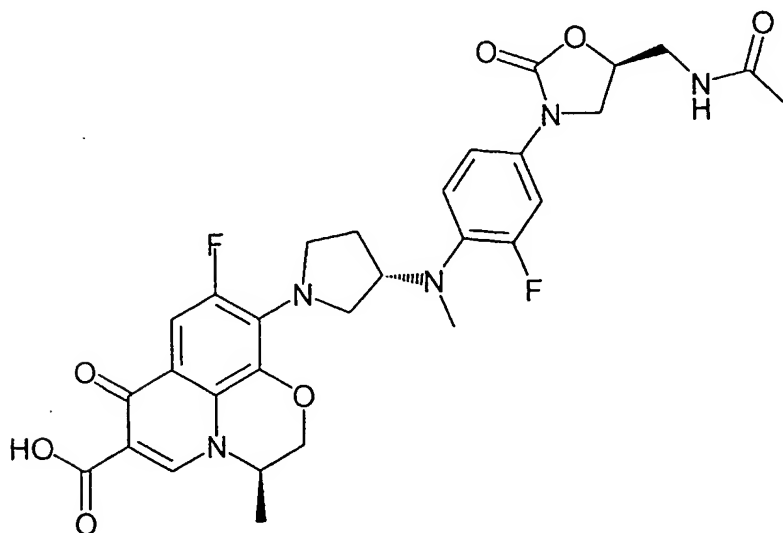
15  $^1\text{H}$ -RMN (DSMO- $d_6$ , 200 MHz,  $\delta$  (ppm)): 8.92 (s, 1H);  
 8.24 (t, 1H, NH); 7.60-7.40 (m, 2H); 7.30-7.10 (m, 2H);  
 4.95-4.80 (m, 1H); 4.80-4.60 (m, 1H); 4.52 (d, 1H); 4.30  
 (d, 1H); 4.10 (t, 1H), 4.00-3.30 (m, 8H); 2.74 (s, 3H);  
 2.20-1.80 (m, 2H); 1.84 (s, 3H); 1.42 (d, 3H).

20

$[\alpha]^{25}_D = -34^\circ$  (c 0.5,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  9/1)

## EXAMPLE 32

9-[3-(S)-({4-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-5 fluoro-3-(R)-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid



Following the procedure described in Example 3 and starting  
 10 with the corresponding chelate obtained by reaction of N-{3-(S)-[3-Fluoro-4-(methyl-pyrrolidin-3-yl-amino)-phenyl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide (obtained following the procedure for the obtention of Reference Example No.27, but replacing 3(R,S)-aminopyrrolidine by 3-  
 15 (S)-aminopyrrolidine) and 8,9-Difluoro-3-(R)-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid boron difluoride chelate (obtained according to Shohgo Atarashi et al., *Chem. Pharm. Bull.* (1987), **35** (5), 1896-1902) the product of the title is obtained.

20

<sup>1</sup>H-RMN (DSMO-d<sub>6</sub>, 200 MHz, δ (ppm)): 8.90 (s, 1H); 8.24 (t, 1H, NH); 7.60-7.40 (m, 2H); 7.36-7.10 (m, 2H); 4.95-4.80 (m, 1H); 4.80-4.60 (m, 1H); 4.54 (d, 1H); 4.24

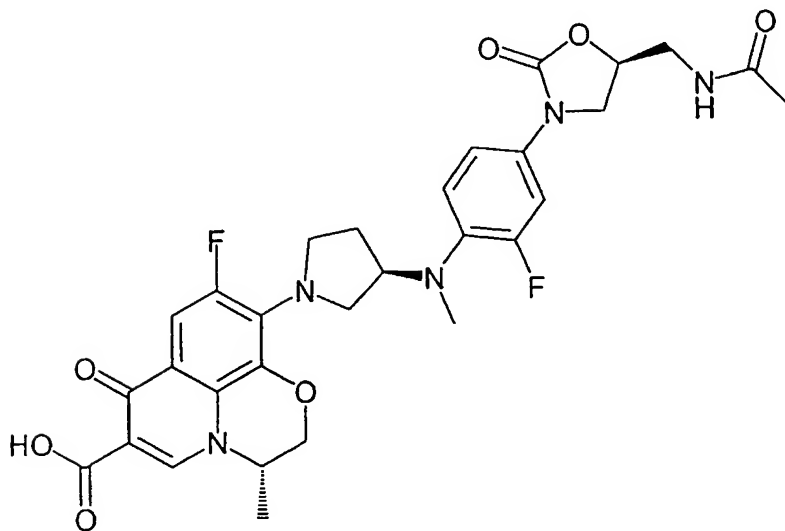
(d, 1H); 4.10 (t, 1H), 4.00-3.30 (m, 8H); 2.74 (s, 3H);  
2.20-1.80 (m, 2H); 1.84 (s, 3H); 1.42 (d, 3H).

$[\alpha]^{25}_D = +66.4^\circ$  (c 0.5,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  9/1)

5

### EXAMPLE 33

9-[3-(R)-({4-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-  
10 3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-  
fluoro-3-(S)-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-  
phenalene-5-carboxylic acid



15

Following the procedure described in Example 3 and starting  
with the corresponding chelate obtained by reaction of N-  
{3-(R)-[3-Fluoro-4-(methyl-pyrrolidin-3-yl-amino)-phenyl]-  
20 2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide (obtained  
following the procedure for the obtention of Reference  
Example No.27, but replacing 3(R,S)-aminopyrrolidine by 3-  
(R)-aminopyrrolidine) and 8,9-Difluoro-3-(S)-methyl-6-oxo-

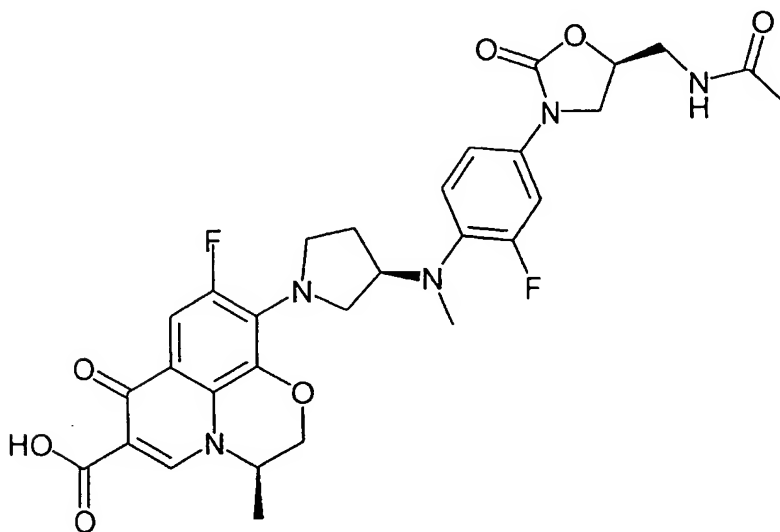
2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid boron difluoride chelate the product of the title is obtained.

<sup>1</sup>H-RMN (DSMO-d<sub>6</sub>, 200 MHz, δ (ppm)): 8.92 (s, 1H); 8.24 (t, 1H, NH); 7.60-7.40 (m, 2H); 7.36-7.10 (m, 2H); 4.95-4.80 (m, 1H); 4.80-4.60 (m, 1H); 4.56 (d, 1H); 4.26 (d, 1H); 4.10 (t, 1H), 4.02-3.30 (m, 8H); 2.76 (s, 3H); 2.20-1.80 (m, 2H); 1.82 (s, 3H); 1.40 (d, 3H).

$[\alpha]^{25}_D = -80.6^\circ$  (c 0.5, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9/1)

#### EXAMPLE 34

9-[3-(R)-({4-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-fluoro-3-(R)-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid





Following the procedure described in Example 3 and starting with the corresponding chelate obtained by reaction of N-{3-(R)-[3-Fluoro-4-(methyl-pyrrolidin-3-yl-amino)-phenyl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide (obtained following the procedure for the obtention of Reference Example No.27, but replacing 3(R,S)-aminopyrrolidine by 3-(R)-aminopyrrolidine) and 8,9-Difluoro-3-(R)-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid boron difluoride chelate (obtained according to Shohgo Atarashi et al., *Chem. Pharm. Bull.* (1987), **35** (5), 1896-1902) the product of the title is obtained.

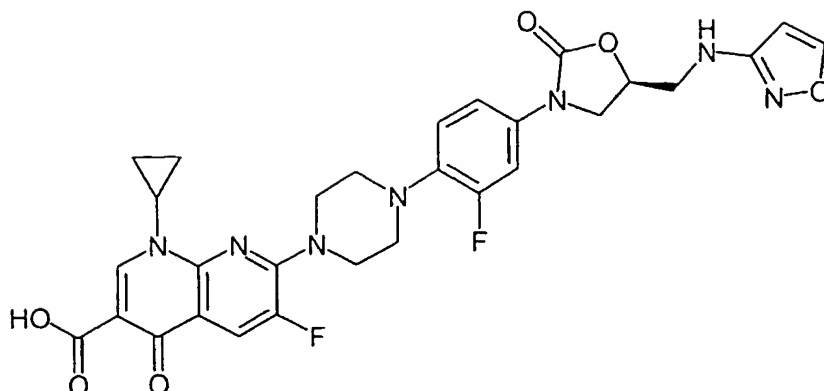
$^1\text{H-RMN}$  (DSMO- $\text{d}_6$ , 200 MHz,  $\delta$  (ppm)): 8.90 (s, 1H); 8.24 (t, 1H, NH); 7.60-7.40 (m, 2H); 7.36-7.10 (m, 2H); 4.95-4.80 (m, 1H); 4.80-4.60 (m, 1H); 4.54 (d, 1H); 4.30 (d, 1H); 4.10 (t, 1H), 4.00-3.30 (m, 8H); 2.72 (s, 3H); 2.20-1.80 (m, 2H); 1.84 (s, 3H); 1.42 (d, 3H).

$[\alpha]^{25}_{\text{D}} = +18^\circ$  (c 0.5,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  9/1)

20

### EXAMPLE 35

1-Cyclopropyl-6-fluoro-7-(4-{2-fluoro-4-[5-(S)-(isoxazol-3-ylaminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid



Following the procedure described in Example 14 and starting with the corresponding product obtained by reaction of the compound in reference Example 25 N-deprotected and 7-Chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid the product of the title is obtained.

<sup>1</sup>H-RMN (DSMO-d<sub>6</sub>, 200 MHz, δ (ppm)): 13.2 (s, 1H); 8.61 (s, 1H); 8.40 (s, 1H); 8.10 (d, 1H); 7.50 (d, 1H); 7.10 (m, 2H); 6.55 (t, 1H); 5.98 (s, 1H); 4.85 (m, 1H); 4.04 (m, 5H); 3.75 (m, 2H); 3.40 (m, 2H); 3.17 (m, 4H); 1.2 (m, 4H).

15

#### EXAMPLES OF PHARMACOLOGICAL RESULTS

Description of the methods used for evaluation of the pharmacological properties

20

The antibacterial activity of the new synthesised compounds on the various strains of the bacterial species was implemented using the technique of microdilution in culture broth according to the regulations of the National Committee for Clinical Laboratory Standards (NCCLS),

(NCCLS. 1993. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M7-A3. NCCLS, Vilanova. PA., and NCCLS. 1993. Methods for dilution antimicrobial susceptibility 5 tests for anaerobic bacteria that grow aerobically. Approved standard M1-A3. NCCLS, Vilanova. PA).

The inoculum used was  $5 \times 10^5$  UFC/ml following dilution of the cultures overnight in the exponential 10 phase of bacterial growth.

The MIC expressed in mg/l was defined as the minimum concentration of antibiotic which inhibited any visible growth.

15

Linezolid was included as comparative compound.

The compounds were tested on the strains of G(+) and G(-) bacteria set out in Table 1, in which:

20

- A: *S. aureus* resistant to meticillin
- B: *E. faecalis* resistant to vancomycin
- C: *S. pneumoniae* resistant to penicillin
- D: *S. agalactiae*
- 25 E: *S. epidermidis*
- F: *S. pyogenes*
- G: *B. fragilis*
- H: *E. coli*
- I: *H. influenzae*
- 30 J: *M. Catarrhalis*.

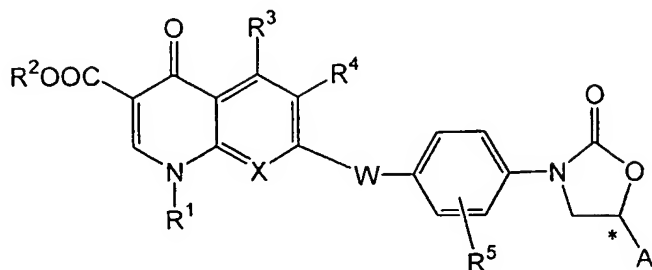
Table 1 – Antibacterial activity on hospital strains (resistant) of Gram (+) and Gram (-) bacteria

5	PRO- DUCT	G (+) strains						Anaerobic	G (-) strains		
		A	B	C	D	E	F		H	I	J
	Linezo- lid	2	2	1	2	1	1	2	>64	16	16
	EXAMP. 1 + 8	0,25	0,125	<0,125	0,125	0,125	<0,125	0,25	8	0,25	0,25
	EXAMP. 3	<0,125	<0,125	<0,125	<0,125	<0,125	<0,125	0,5	64	4	0,5
	EXAMP. 4	0,25	0,25	<0,125	<0,125	<0,125	<0,125	0,5	16	2	1
	EXAMP. 5	0,5	0,5	0,5	0,5	0,25	0,5	2	4	1	1
	EXAMP. 6	2	1	1	0,5	0,5	1	16	2	<0,125	0,25
	EXAMP. 7	0,25	0,5	0,25	0,5	0,25	0,25	2	8	4	1
	EXAMP. 9	<0,125	<0,125	<0,125	<0,125	<0,125	<0,125	0,5	>64	1	0,25
	EXAMP. 10	1	2	1	1	0,25	1	4	64	4	2
	EXAMP. 11	0,5	0,5	0,5	1	0,125	0,5	1	32	4	1
	EXAMP. 16	4	2	1	1	2	1	8	>64	>64	8
	EXAMP. 17	2	2	0,5	0,5	1	1	4	>64	64	4
	EXAMP. 19	4	8	4	8	4	8	>64	32	1	2
	EXAMP. 20	1	2	1	1	0,50	1	>64	>64	2	4
	EXAMP. 21	0,25	<0,125	<0,125	<0,125	<0,125	<0,125	0,25	64	2	0,5
	EXAMP. 22	<0,125	<0,125	0,25	<0,125	<0,125	<0,125	0,5	64	2	0,5

CLAIMS

1. Compound of general formula (I):

5



(I)

10 wherein:

X: CR<sup>6</sup> or N;

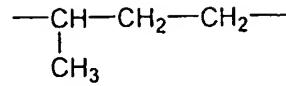
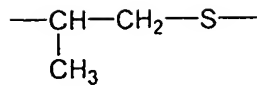
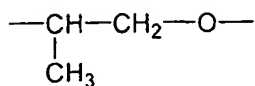
R<sup>1</sup>: alkyl C<sub>1</sub>-C<sub>4</sub>, cycloalkyl C<sub>3</sub>-C<sub>6</sub>, alkenyl C<sub>2</sub>-C<sub>4</sub>, 2-hydroxyethyl, 2-fluoroethyl, or phenyl optionally substituted by 1 or 2 atoms of fluorine;

R<sup>2</sup>: H, alkyl C<sub>1</sub>-C<sub>4</sub> or phenyl;

20 R<sup>3</sup>: H, halogen, alkyl C<sub>1</sub>-C<sub>4</sub>, or alkoxy C<sub>1</sub>-C<sub>4</sub>, amino;

R<sup>4</sup>: H or halogen;

R<sup>6</sup>: H, halogen, alkyl C<sub>1</sub>-C<sub>4</sub>, haloalkoxy C<sub>1</sub>-C<sub>4</sub>, or  
25 else R<sup>1</sup> and R<sup>6</sup> together form a bridge of structure



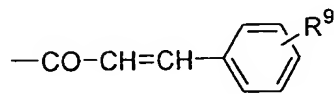
R<sup>5</sup>: H, halogen, OCH<sub>3</sub>, alkoxy C<sub>1</sub>-C<sub>4</sub>, alkyl C<sub>1</sub>-C<sub>4</sub>, or haloalkyl C<sub>1</sub>-C<sub>4</sub>;

5

A: -CH<sub>2</sub>-NH-R<sup>7</sup>, -CHOH-C≡CH;

wherein

10 R<sup>7</sup>: isoxazol, -CO-R<sup>8</sup>, -CS-R<sup>8</sup>, -CS-OR<sup>8</sup>, -COOR<sup>8</sup>, -CONHR<sup>8</sup>, -CSNHR<sup>8</sup>, -SO<sub>2</sub>-R<sup>8</sup> or



15

wherein

R<sup>8</sup>: alkyl C<sub>1</sub>-C<sub>4</sub>, haloalkyl C<sub>1</sub>-C<sub>4</sub>, alkenyl C<sub>2</sub>-C<sub>4</sub>, aryl, alkyl C<sub>1</sub>-C<sub>4</sub> substituted by an alkoxy group C<sub>1</sub>-C<sub>4</sub>, carboxyalkyl C<sub>1</sub>-C<sub>4</sub>, cyano, or amino;

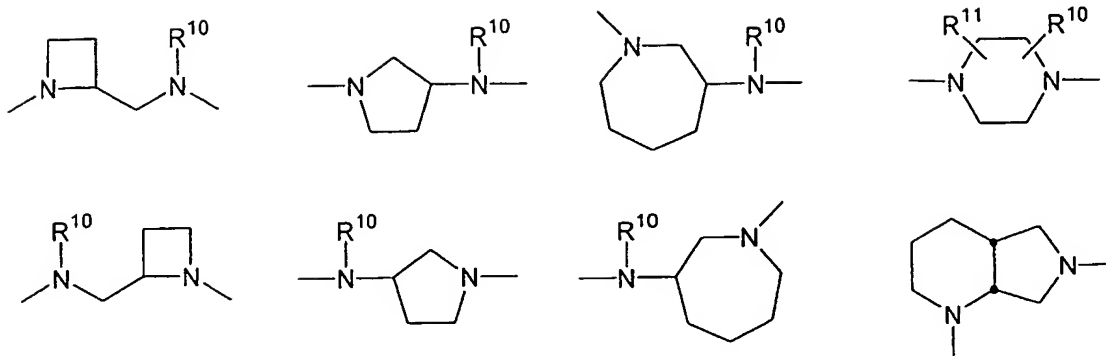
20

R<sup>9</sup>: H, alkyl C<sub>1</sub>-C<sub>4</sub>, alkenyl C<sub>2</sub>-C<sub>4</sub>, OH, alkoxy C<sub>1</sub>-C<sub>4</sub>, NR<sup>12</sup>R<sup>13</sup>, NO<sub>2</sub>, halogen, or CO-R<sup>12</sup>;

R<sup>12</sup> and R<sup>13</sup>: independently, H or alkyl C<sub>1</sub>-C<sub>4</sub>;

25

W:



wherein

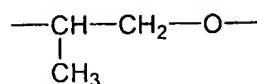
R<sup>10</sup> and R<sup>11</sup> are independently H, or alkyl C<sub>1</sub>-C<sub>4</sub>;

5

a pharmaceutically acceptable salt or solvate, or any geometric isomer, optical isomer or mixture of isomers thereof in any proportion or polymorph thereof.

10 2. Compound according to Claim 1, characterised in that R<sup>1</sup> is cyclopropyl, ethyl, 2-fluoroethyl, phenyl or difluorophenyl, or else R<sup>1</sup> and R<sup>6</sup> together form a bridge of structure:

15

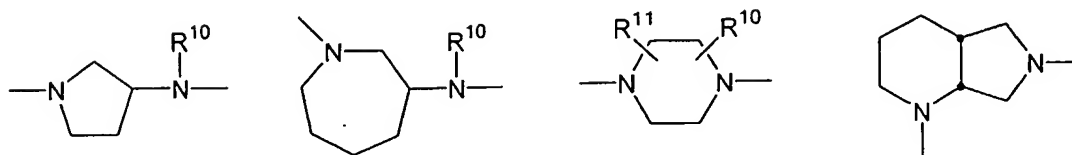


3. Compound according to Claim 1, characterised in that R<sup>6</sup> is H, CH<sub>3</sub>, OCH<sub>3</sub>, OCHF<sub>2</sub>, F or Cl.

4. Compound according to Claim 3, characterised in  
20 that R<sup>6</sup> is H or F.

5. Compound according to Claim 1, characterised in that R<sup>4</sup> is F or Cl and R<sup>3</sup> is H.

6. Compound according to Claim 1, characterised in that W is



5 wherein  $R^{10}$  and  $R^{11}$  are as defined in Claim 1.

7. Compound according to Claim 1, characterised in that the C5 of oxazolidinone ring has an (S) configuration when  $A = -CH_2-NH-R^7$  and (R) when  $A = -CHOH-C\equiv CH$ .

10

8. Compound according to claims 1 to 6, characterised in that it is selected from one of the following:

- 15 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 7-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-azepan-1-yl]-1-
- 20 cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 25 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-
- 30 dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid



- 9-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid
- 5 - 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid
- 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 10 - 1-cyclopropyl-7-[4-(4-{5-(S)-[(3-ethyl-ureido)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 15 - 1-cyclopropyl-7-(4-{4-[5-(S)-(ethoxycarbonylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 1-cyclopropyl-6-fluoro-7-[4-[2-fluoro-4-(5-(S)-{[3-(4-fluoro-phenyl)-acryloylamino]-methyl}-2-oxo-oxazolidin-3-yl)-phenyl]-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 20 - 1-cyclopropyl-7-[4-(4-{5-(S)-[(3-ethyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 25 - 1-(2,4-difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-5-[5-(R)-(1-(R,S)-hydroxy-prop-2-ynyl)-2-oxo-oxazolidin-3-yl]-phenyl}piperazin-1-yl)-4-oxo-1,4-dihydro-
- 30 [1,8]naphthyridine-3-carboxylic acid ethyl ester
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid ethyl ester

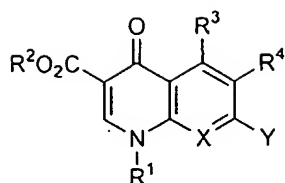
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester
- 5 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6,8-difluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 1-(2,4-Difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-
- 10 (S)-(isoxazol-3-ylaminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester
- 1-(2,4-difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-
- (R)-(1-hydroxy-prop-2-ynyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-
- 15 [1,8]naphthyridine-3-carboxylic acid
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-
- 20 3-carboxylic acid
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid
- 25 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6,8-difluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 1-(2,4-Difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-
- 30 (S)-(isoxazol-3-ylaminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid
- 1-ethyl-6,8-difluoro-7-[4-(2-fluoro-4-[5-[(3-methylthioureido)-methyl]-2-oxo-oxazolidin-3-yl]-phenyl)-

- piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{2-oxo-5-(S)-[(3-propyl-thioureido)-methyl]-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
  - 5 - 1-cyclopropyl-6-fluoro-7-[4-{2-fluoro-4-[5-(S)-(methanesulfonylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
  - 10 - 7-(4-{4-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-1-ethyl-6,8-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
  - 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{2-oxo-5-(S)-[(2,2,2-trifluoro-acetylamino)-methyl]-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
  - 15 - 7-(4-{4-[5-(S)-(benzoylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro 4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
  - 20 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
  - 25 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
  - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-
  - 30 difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
  - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-

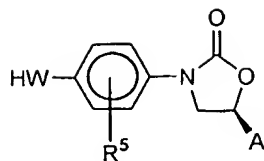
- difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
- 5
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 10
- 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid methyl ester
- 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid ethyl ester
- 15
- 9-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid methyl ester
- 20
- 9-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid ethyl ester
- 25
- 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid methyl ester
- 30
- 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid ethyl ester

- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
- 5 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
- 10 - 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 15 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid methyl ester
- 20 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6,8-difluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
- 25 - 1-Ethyl-6,8-difluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester

30           9. Process for obtaining a compound of general formula (I), according to Claim 1, characterised in that it comprises the reaction of a compound of general formula (II) with a compound of general formula (III):



(II)

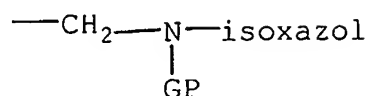


(III)

wherein:

A' is:

- 5        a)  $-\text{CH}_2-\text{NH}-\text{R}^7$   
           b)  $-\text{CHOH}-\text{C}\equiv\text{CH}$   
           c)

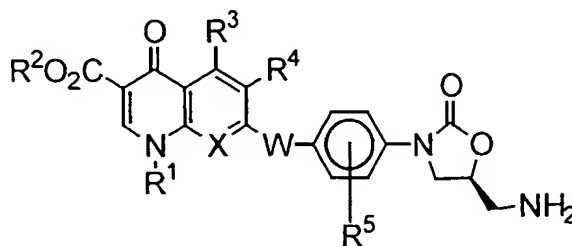


10        Y is an leaving group, such as an atom of halogen (F, Cl, Br, I), a tosylate or mesylate group, and the like;

          R¹, R², R³, R⁴, R⁵, X and W have the meaning defined in Claim 1;

15        GP is a protecting group of amines.

10. Process for obtaining a compound of general formula (I), according to Claim 1, in which A is  $-\text{CH}_2-\text{NH}-\text{R}^7$  and R⁷ is different from isoxazole, characterised in that it  
 20 comprises the reaction of a compound of formula (V)



(V)

wherein R¹, R², R³, R⁴, R⁵, X and W have the meaning

defined in Claim 1.

with a compound of formula (VI) or with a compound of formula (VII)

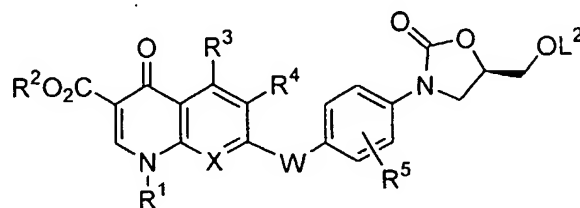


wherein L is a good leaving group, such as an atom of halogen (F, Cl, Br, I), a tosylate or mesylate group, and the like;

Z is Oxygen or Sulphur, and

10  $R^7$  and  $R^8$  have the meaning defined in Claim 1, with  $R^7$  being different from isoxazol.

11. Process for obtaining a compound of general formula (I), according to Claim 1, in which A is  $-CH_2-NH-R^7$   
 15 and  $R^7$  is isoxazol, characterised in that it comprises the reaction of a compound of general formula (VIII):



(VIII)

20

wherein

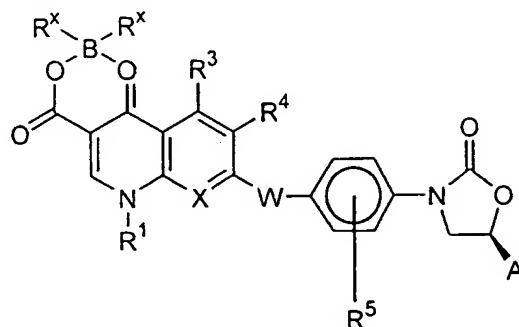
-  $OL^2$  represents a good leaving group, such as a residue of aryl or methyl sulphonic acid, substituted or not substituted, preferably by a tosylate or mesylate  
 25 group;

-  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ , X and W have the meaning defined in Claim 1;

with isoxazolil-3-amine, the amine group being protected with a protecting group of amines.

30

12. Process for obtaining a compound of general formula (I), according to Claim 1, in which  $R^2$  is hydrogen, characterised in that it comprises the hydrolysis of a boron chelate of formula (IX)



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(IX)

wherein

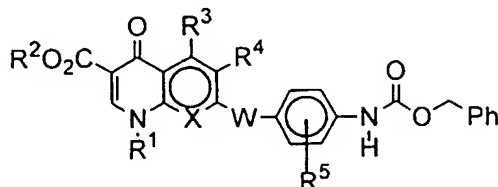
$R^x$  can be F or  $\text{CH}_3\text{COO}-$ ;

10        A,  $R^1$ ,  $R^3$ ,  $R^4$ ,  $R^5$ , X and W have the meaning defined in Claim 1.

13. Process for obtaining a compound of general formula (I), according to Claim 1, in which A is

15         $-\text{CHOH}-\text{C}\equiv\text{CH}$

characterised in that it comprises the reaction of a compound of formula (IV)



(IV)

20

wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ , X and W have the meaning defined in Claim 1,

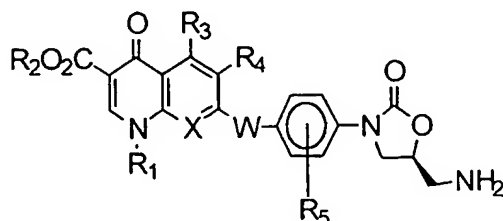


with 2,3-hydroxy-pent-4-ynyl p-toluenesulphonate.

14. Process as claimed in any of claims 11 to 13, characterised in that it comprises subjecting the product 5 obtained, optionally, to one or more of the following final steps:

- a) Conversion of a compound of general formula (I) into another compound of general formula (I);
- b) Elimination of the protecting group;
- 10 c) Preparation of a pharmacologically acceptable salt of a compound of formula (I) and/or a pharmacologically acceptable solvate thereof.

15. Compound of formula (V)

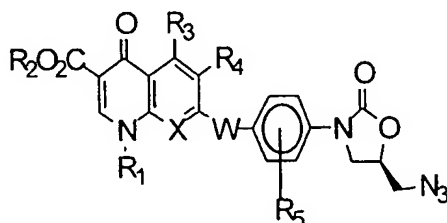


15

(V)

wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ , X and W have the meaning defined in Claim 1.

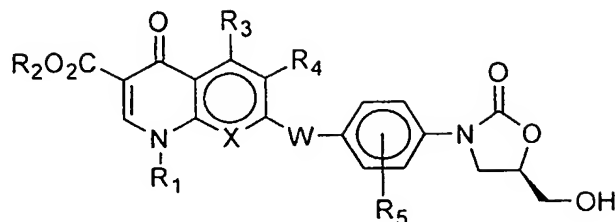
20 16. Compound of formula (X)



(X)

wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ , X and W have the meaning defined in Claim 1.

17. Compound of formula (XI)



5

(XI)

wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $X$  and  $W$  have the meaning defined in Claim 1.

10 18. Pharmaceutical composition which comprises a compound of general formula (I) according to any of claims 1 to 8, for use as a medicament.

15 19. Use of a compound of general formula (I), according to any of claims 1 to 8, for the preparation of a pharmaceutical composition for treating microbial infections in humans or warm-blooded animals.

20 20. Pharmaceutical composition which comprises a compound of general formula (I) according to any of claims 1 to 8 in a therapeutically active quantity and with a suitable quantity of at least one excipient.

25

## INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/IB 02/02408

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D413/14 A61K31/422 A61P31/04 C07D471/04

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR 2 403 339 A (BELLON LABOR SA ROGER) 13 April 1979 (1979-04-13) claim 1	1-20
A	WO 97 37980 A (BARBACHYN MICHAEL R ;UPJOHN CO (US); FLECK THOMAS J (US); HOUSER D) 16 October 1997 (1997-10-16) claim 1	1-20
A	WO 98 01447 A (DARBYSHIRE CATHERINE JANE ;ZENECA LTD (GB); BETTS MICHAEL JOHN (GB) 15 January 1998 (1998-01-15) claim 1	1-20
A	WO 93 23384 A (UPJOHN CO ;HUTCHINSON DOUGLAS K (US); BRICKNER STEVEN JOSEPH (US);) 25 November 1993 (1993-11-25) claim 1	1-20
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*G\* document member of the same patent family

Date of the actual completion of the international search

11 September 2002

Date of mailing of the international search report

25/09/2002

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Authorized officer

Baston, E

## INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/IB 02/02408

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 878 194 A (SANKYO CO ;UBE INDUSTRIES (JP)) 18 November 1998 (1998-11-18) claim 1 ---	1-20
A	HAYAKAWA I ET AL: "SYNTHESIS AND ANTIBACTERIAL ACTIVITIES OF SUBSTITUTED 7-OXO-2,3-DIHYDRO-7H-PYRIDOU1,2,3-DEU1,4BE NZOXAZINE-6-CARBOXYLIC ACIDS" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 32, no. 12, 1 December 1984 (1984-12-01), pages 4907-4913, XP000654032 ISSN: 0009-2363 table 1 -----	1-20

## INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No

PCT/IB 02/02408

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			JP 5406686 A	29-05-1979
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